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DRUG ALLERGY

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The phenomena of idiosyncrasy to drugs have long presented a problem to physicians, but it is only recently that progress has been made in elucidation of the mechanism of many of these reactions. A considerable number of reactions are due to immunologic hypersensitivity or allergy, unrelated to the drug action. The recognition of allergic manifestations as such is made more difficult by the pharmacologic activity of these agents, and in some cases the distinction between allergic and toxic reactions cannot be made with certainty.

PATHOLOGIC CHANGES

In recent years, numerous studies of the histologic lesions of drug hypersensitivity, as distinguished from toxic effects, have been reported. Arteritis, with localized fibrinoid and hyaline degeneration of the media and perivascular infiltration, has been described in allergy to a number of different drugs.[1] Focal necrosis of the myocardium, liver, spleen and other organs, with infiltration of mononuclear cells, is also characteristic. The monocytic infiltration may produce granulomas of these organs or, in the heart, extensive interstitial myocarditis.[2] Figure 1 shows arteritis due to sulfadiazine, and figure 2 shows granuloma of the liver due to sulfadiazine. A similar monocytic infiltration of the periportal spaces of the liver due to arsphenamine sensitization may be associated with obstruction of the bile canaliculi causing jaundice.[3] There is also evidence that massive parenchymal necrosis of the liver due to arsphenamine, cinchophen and sulfonamide drugs may represent a sensitization phenomenon.

SYMPTOMS

The symptoms of drug allergy are varied; some, such as asthma, urticaria, contact dermatitis and anaphylactic shock, are readily recognized as allergic manifestations, while others, such as fever, leukocytosis, arthralgia and morbilliform and scarlatiniform rashes, are easily confused with the symptoms of infectious diseases.

The most dramatic of allergic manifestations, anaphylactic shock, is familiar as a reaction to the injection of heterologous antiserum into sensitive patients. Similar reactions (occasionally fatal) may be produced by injections of other protein-containing biologic products, such as liver extract, insulin, toxoids and vaccines, and occasionally by the intravenous injection of such nonprotein drugs as arsphenamine, quinine and thiamine. These reactions may occur unexpectedly, but often mild evidences of sensitivity will follow one or two injections before the occurrence of a severe anaphylactic reaction; these should suggest caution in administering further injections.

Asthma and rhinitis due to drug allergy are not unusual, most often affecting persons who also have the same symptoms from other causes. The drug most frequently causing these symptoms is aspirin (acetylsalicylic acid), but sulfonamide drugs, penicillin, quinine, arsphenamine, vegetable gums and protein drugs, such as pancreatin and papain, are occasional causative agents. Attacks of asthma caused by acetylsalicylic acid usually start within a few minutes, because of its solubility and diffusibility, so that the relationship of cause and effect is apparent. The severity of the attacks is such that in several cases death has resulted from ingestion of 5 to 10 grains (0.3 to 0.6 Gm.). Cutaneous tests are not helpful in such sensitivity to crystalloid drugs. In the case of asthma and rhinitis due to vegetable gums and proteins, scratch or intracutaneous tests are diagnostic. Sensitizations to the vegetable gums are of practical importance because of the use of gums as excipients or cohesive agents in the preparation of pills. Most pills contain one of the gums, the presence of which is usually disregarded, and the possibility must be considered that a reaction following their use may be due to allergy to the gum rather than the pharmacologically active ingredient.[4]

Drugs of practically all types, crystalloids, proteins and gums, may cause urticaria and angioedema. In recent years the drug most frequently causing urticaria has been penicillin. Urticaria due to penicillin may occur as the sole manifestation of sensitization or may form a part of a syndrome resembling serum sickness in every respect, with urticaria, fever and arthralgia. The reaction is usually delayed seven to ten days after the first dose and frequently two or three days after use of the drug is discontinued. If the penicillin has been injected in oil and wax, the general features of the reaction are similar, but, in addition, there is usually a pronounced swelling at the site of injection, due to persistence of antigen at that location.

Fever due to drugs is an important and confusing manifestation of drug allergy, most frequently seen after administration of sulfonamide drugs, but also caused by

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1. Rich, A. R.: The Role of Hypersensitivity in Periarteritis Nodosa, Bull. Johns Hopkins Hosp. **71**: 123, 1942.
2. Simon, M. A.: Pathologic Lesions Following the Administration of Sulfonamide Drugs, Am. J. M. Sc. **205**: 439, 1943.
3. Hanger, F. M., Jr., and Gutman, A. B.: Postarsphenamine Jaundice Apparently Due to Obstruction of Intrahepatic Biliary Tract, J. A. M. A. **115**: 263 (July 27) 1940.
4. Brown, E. B., and Crepea, S. B.: Allergy (Asthma) to Ingested Gum Tragacanth, J. Allergy **18**: 214, 1947.

penicillin, streptomycin, thiouracil, iodides and other drugs. During the first course of any of these drugs, fever usually appears abruptly on the seventh to tenth day. The temperature may rise to 105 or 106 F., and the leukocyte count may remain normal or rise as high as 30,000. The fever is frequently, but not always,

Fig. 1.—Arteritis following use of sulfathiazole (from Dr. Arnold Rich).

accompanied with morbilliform or scarlatiniform rash and may be easily mistaken for one of the acute infectious diseases. In cases in which the sulfonamide drugs have been used for pneumonia or pyogenic infection, the sudden rise of temperature, if accompanied with leukocytosis and not a rash, suggests a spread of infection. Such a misinterpretation may lead the physician to continue or increase the dose of the sulfonamide drug and occasionally has resulted in death from sensitivity due to drugs.[5] The diagnosis of drug fever is rarely easy, but if one keeps in mind the possibility of its occurrence, the characteristic incubation period of seven to ten days and the rash and leukocytosis which may or may not accompany it, it may be suspected and a suitable substitute made for the previous medication.

When use of the causative drug is discontinued, the fever subsides in two or three days. The patient remains sensitive for a considerable period, and a single subsequent dose may cause an abrupt rise of temperature within a few hours. The administration of sulfonamide drugs for two to five days may initiate the process of sensitization, though the drug may be eliminated from the body before fever develops. Subsequent administration of the same drug will then cause an immediate reaction.

In the case of drugs injected once or twice a week, such as arsphenamine and oxophenarsine hydrochloride, drug fever occurs abruptly after the second or third injection, producing the picture of Milian's "syndrome of the ninth day."[6]

Drug fever is rarely serious if recognized as such and use of the causative agent discontinued, but it is an indication that sensitization has taken place and further use of the same or closely related drugs may give rise to more serious manifestations of drug allergy.

Rashes due to drugs are the commonest manifestations of drug allergy. Their morphologic appearances are exceedingly varied, some forms being characteristic of certain types of drugs, as the acneform dermatitis produced by bromides and iodides, while others, such as the morbilliform rashes following internal medications and vesicular contact dermatitis, may be due to a wide variety of agents.

When the drug, such as one of the sulfonamide drugs, is given in a continuous course, the morbilliform rash most often appears on the seventh to fourteenth day, often accompanied with drug fever. If use of the drug is stopped, the rash fades promptly, but if it is continued the eruption usually becomes more intense and may progress to an exfoliative dermatitis which is exceedingly persistent even after administration of the drug has been discontinued. Once the skin has been sensitized, subsequent use of the drug may cause a

Fig. 2.—Granuloma of the liver following use of sulfadiazine.

5. Lederer, M., and Rosenblatt, P.: Death During Sulfathiazole Therapy: Pathologic and Clinical Observations on Four Cases with Autopsies, J. A. M. A. **119**: 8 (May 2) 1942.

6. Peters, E. E.: Syndrome of Milian's Erythema of the Ninth Day, Am. J. Syph., Gonor. & Ven. Dis. **25**: 527, 1941.

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prompt appearance of an intense confluent eruption and topical application of the drug may cause vesicular contact dermatitis.

Sensitization of the skin may also be initiated by topical application, continued local use of such drugs as the sulfonamide preparations for two weeks or more frequently causing contact dermatitis.[7] If the same drug is subsequently administered by mouth there is usually a prompt recurrence of dermatitis at the sites of previous contact. In a considerable number of patients this local recurrence is accompanied with constitutional symptoms, such as chills, fever and eosinophilia,[7] indicating that surface contact has produced a systemic rather than merely a cutaneous sensitization.

Jaundice may occur after the administration of a wide variety of drugs. In certain instances, as with chloroform and carbon tetrachloride, there is little doubt that damage to the liver is a normal toxic effect of the drug. In the case of other drugs, such as sulfonamide preparations, arsphenamine, cinchophen and quinacrine hydrochloride, there is reason to believe that jaundice occurs as a result of sensitization. Hanger and Gutman [8] pointed out that jaundice occurring early in the course of arsphenamine treatment and showing the blood chemical observations of obstructive jaundice is presumably due to drug sensitivity. It is probable that drug sensitivity can also cause nonobstructive jaundice, but series of cases of postarsphenamine jaundice to which these chemical criteria have not been applied undoubtedly include cases of coincidental infectious hepatitis and of homologous serum jaundice transferred by the technic of injecting the drug, so that results based on them must be interpreted with caution.

All of the drugs causing jaundice are also common causes of other manifestations of allergy, such as drug fever and cutaneous rashes, and not infrequently jaundice occurs with or follows soon after one of these evidences of sensitization. When a drug is given in an interrupted course, jaundice is more frequent in the second course, suggesting that sensitivity has been acquired. After one attack of jaundice, further use of the same drug is apt to cause a recurrence.

Another type of dangerous reaction to drugs which has been suspected of having an allergic mechanism is granulocytopenia caused by such drugs as aminopyrine, thiouracil, arsphenamine and the sulfonamide preparations. Agranulocytosis may occur suddenly in patients who have previously tolerated the same drug for weeks or months, or after a gradually developing leukopenia. If recovery occurs, a subsequent dose of the causative drug may produce a decided drop in the leukocyte count within a few hours. Dameshek and Colmes [8] reported positive cutaneous reactions to a mixture of aminopyrine and human serum in 3 patients suffering from agranulocytosis due to that drug. These observations are suggestive of an allergic mechanism, but have not yet received adequate confirmation.

Granulocytopenia due to drugs is occasionally accompanied with thrombopenia, which may also occur as a separate reaction to the sulfonamide drugs, arsephenamine and to other drugs, but most often to the hypnotic sedormid® (allyl-isopropyl-acetyl-carbamide). Thrombopenia caused by drugs is usually manifested by purpura appearing abruptly after prolonged use of the drug. After one such attack, further administration of the same drug usually causes a prompt recurrence.

DIAGNOSIS AND MANAGEMENT

Most forms of allergy to protein drugs are readily demonstrable by scratch or intracutaneous tests with the causative agent. In allergy to nonprotein crystalloid drugs, such tests are rarely helpful. Since the antigenic activity of crystalloid drugs is believed to result from combination with proteins within the body, a few workers have used drug azoproteins as antigens for cutaneous tests, but the results reported have been disappointing. Leftwich [9] reported success in the use of serum of patients receiving full doses of sulfonamide drugs as antigens in intracutaneous tests for the diagnosis of sensitivity to sulfonamide drugs. No confirmation of this work has been published, and Fink, Burton and Wheeler [10] reported negative results from the use of this method in children. The writer has performed this test on patients known to be highly sensitive to sulfadiazine, with uniformly negative results. It is not a reliable criterion of sensitization to sulfonamide drugs. The only type of cutaneous test with nonprotein drugs which has proved of diagnostic value is the patch test in contact dermatitis. Frequently the patch test is also helpful in the diagnosis of dermatitis resulting from internal medication, but it is less reliable in such cases, because of the uncertainty of absorption of drugs through the intact skin.

In general the diagnosis of drug allergy depends on a knowledge of the clinical manifestations of sensitivity which may be expected from each drug used. The history of a hereditary tendency to allergic disease is of little aid in diagnosis except of those reactions manifested by asthma, rhinitis and urticaria. Many of the more serious types of drug allergy may be avoided if minor symptoms of sensitization, such as cutaneous rashes and fevers due to drugs, are recognized as such and use of the causative drug is promptly discontinued.

The specificity of drug allergies varies so greatly that it is impossible to predict the results of substitution of a closely related drug for one which has produced a reaction. Some patients react to a whole group of chemically related compounds, while others show a sensitivity specific for one drug of the group. Only a cautious trial with a fraction of the usual dose will give the answer in an individual case.

Likewise, the duration of drug sensitization is exceedingly variable, in some instances lasting for years and in others, especially in sensitization to penicillin, ending within a few weeks. If an acceptable substitute is available, the wisest procedure is to avoid readministration of a drug which has once caused an allergic reaction for an indefinite period. Occasionally strong indications for the use of an important drug may outweigh the history of allergic reactions to previous administration, and cautious trial, starting with a fractional dose, is warranted. In the case of penicillin,

7. Sulzberger, M. B.; Kanof, A.; Baer, R. L., and Lowenberg, C.: Sensitization by Topical Application of Sulfonamides, J. Allergy **18**: 92, 1947.

8. Dameshek, W., and Colmes, A.: The Effect of Drugs in the Production of Agranulocytosis, with Particular Reference to Amidopyrine Hypersensitivity, J. Clin. Investigation **15**: 85, 1936.

9. Leftwich, W. B.: An Intradermal Test for the Recognition of Hypersensitivity to the Sulfonamide Drugs, Bull. Johns Hopkins Hosp. **74**: 26, 1944.

10. Fink, H. W.; Burton, I., and Wheeler, W.: The Applicability of Skin Tests for Sulfonamide Hypersensitivity in Children, J. Immunol. **54**: 65, 1946.

such attempts are often successful; with the sulfonamide drugs, the results are less favorable.

While desensitization is often possible with protein compounds, attempts at desensitization with nonprotein drugs are rarely successful and occasionally cause severe reactions. In general substitution of another medication is preferable.

SUMMARY

Many of the untoward reactions to drugs, such as anaphylactic shock, asthma, rhinitis, urticaria, arthralgia, drug fever, dermatitis and probably hepatitis, granulocytopenia and thrombopenia, are due to allergic sensitization. Pathologic studies have demonstrated widespread visceral lesions in patients with clinical evidence of drug allergy. Scratch and intracutaneous tests with nonprotein drugs are rarely diagnostic. Patch tests are of value in contact dermatitis and occasionally in other eruptions due to drugs. The diagnosis of drug allergy in most cases must depend on the history and physical manifestations. Recognition of early signs of sensitization and discontinuation of use of the causative drug will often avoid the more serious types of reaction.

ABSTRACT OF DISCUSSION

DR. MARION B. SULZBERGER, New York: Rashes are the commonest manifestations of drug allergies. It is therefore not astonishing that the older dermatologic literature is where one must look to get the historical background of this important chapter of medicine. In 1877 Dr. Prince Morrow of New York published one of the best treatises on rashes and eruptions due to drugs. In 1893 Josef Jadassohn published a monograph entitled "Medicamentous Dermatitis," an almost prophetic treatise in which almost everything we know today is discussed. Simple chemicals of relatively low molecular weight, chemicals which can be synthesized in the laboratory, even elements such as mercury, can induce almost every known form of immunologic change. As a result, in studying the basic phenomena of immunology, one need not employ as antigens the impure mixtures and complex inconstant combinations derived from nature. The second important point is that almost every known disease picture can be caused by the immunologic reactions to such simple chemicals. In other words, there is nothing pathognomonic for disease produced by a living micro-organism, as distinguished from disease elicited by simple nonliving chemical substances. Thus, identical forms of arthritis, urticaria, asthma, erythematous eruptions, rhinitis and fever can be caused by infecting living agents, by "protein" allergens and also by salicylates and many simple chemicals. Hepatitis can be due to a virus, on one hand, to a drug allergy, on the other hand, to direct toxic action, such as that of chloroform, or to combinations of these. One of the most illuminating prospects in all medicine is offered by the study of the reasons for these frequent similarities of the disease pictures caused by living agents and by nonliving chemicals. Dermatologists' combined studies of cutaneous diseases and cutaneous reactions due to simple chemicals and drugs and the diseases and cutaneous reactions due to living micro-organisms have made clearer one great fact. Many important micro-organisms, such as tubercle bacilli, lepra bacilli, spirochetes and dermatophytic fungi, produce disease not by forming toxins, but by producing allergens which specifically sensitize the tissues. The picture the physician sees is mainly the result of the immunologic reaction of the sensitized tissue to the products of the micro-organisms. With this concept in mind, one can begin to comprehend the similarities of the disease pictures produced by certain living agents and those produced by simple chemical allergens. Both are based on analogous immunologic alterations, and, more important, both can and must be studied by related and integrated theoretical concepts and experimental approaches.

DR. HOWARD OSGOOD, Buffalo: While Dr. Sherman considered a number of drugs, I should like to add one more. This is papain, derived from the fruit of the papaya tree or East Indian paw paw. The omission is undoubtedly due to the fact that sensitivity to it is not the usual so-called drug sensitivity, but is of the atopic type. Papain is a powerful protein digestant and occurs as a powdered extract in many proprietary and other digestant mixtures sold in drug stores. Papaya is used as a meat tenderizer in hamburger and other ground meats, being introduced shortly before cooking. It is used in treating hides. It is used extensively as a clarifier in beer and ale, although the amount present is in large dilution. The juice is canned and sold for drinking. In persons sensitive to it, exposure produces vasomotor rhinitis and asthma, which may be severe, and digestive symptoms.

DR. THEODORE LOUIS SQUIER, Milwaukee: It would be most most helpful if determinations of aminopyrine sensitivity or of sensitivities to other drugs were possible by a cutaneous test such as that described by Dameshek and Colmes, or by some modification thereof, such as was described by Leftwich. My co-workers and I have used the cutaneous test procedure advocated by Dameshek and Colmes, i. e., mixing of aminopyrine with human serum and later testing patients intracutaneously with the drug-serum mixture, with consistently negative results. Likewise, in a fairly extensive series of patients known to be sensitive to sulfonamide drugs, we have made cutaneous tests as described by Leftwich, using blood serum with a high content of a sulfonamide drug from patients treated with sulfonamide preparations. The results were uniformly negative. It is important to emphasize that when cutaneous tests are done with any serum, one may be confused by false positive reactions due to isoantibodies in the serum. Any one who has done passive transfer tests will recall how frequently the reactions are observed to the serum used in sensitizing the skin sites.

DR. J. A. RUDOLPH, Miami Beach, Fla.: I have under observation a group of patients who have been sensitized by the sulfonamide drugs, penicillin and some of the antihistaminics. I have not been able to determine whether these sensitizations have remained latent or not, since the patients meet none of the usual criteria for an allergic person. Could this not be the reason why one sees more allergic persons today who have asthma, rhinitis or other allergies which may have been initiated by the various drugs in question? It would seem that the immunologic concept of allergy may also be one of precipitation by drugs and need not be dependent on heredity and the other allergic criteria, alone, as we believe at present.

DR. W. B. SHERMAN, New York: I agree with essentially all the points brought out, and particularly Dr. Squier's remarks that no form of cutaneous test is reliable in the diagnosis of sensitivity to drugs. The diagnosis must be made from the knowledge of the particular reaction to be expected from each drug. I would like to stress, also, that some of the apparently minor reactions, such as cutaneous rashes and drug fever, may be warnings that more serious manifestations will take place if use of the drug is continued.

Mrs. John Hunter.—It was about this time that Hunter, at the age of 43, married Anne Home, the daughter of an Army doctor, and 29 years of age. She was a woman of great charm and considerable social distinction, the friend of Haydn, Madame d'Arblay and Mrs. Montague. She was something of a poetess and wrote the words for Haydn's "The Creation."—Souttar, H.S., The Hunterian Oration, *Annals of the Royal College of Surgeons of England*, March 1949, page 127.

PATHOGENESIS OF ARTERIAL HYPERTENSION

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Much is known of the pathogenesis of spontaneous hypertension in human beings and experimental hypertension in animals, despite the short time during which modern investigative methods have been used. Because the various types of experimental renal hypertension have received the greatest share of study is insufficient reason for one's assuming that they necessarily mirror more exactly essential hypertension in human beings. Several years ago, some clinicians overstepped judicious bounds in proclaiming that the cause of human hypertension had been reproduced in animals, a view wisely not expressed at that time by the inspirer of some of this work, Harry Goldblatt. But there are certainly enough similarities between experimental renal hypertension and essential hypertension to justify the hope that elucidation of the mechanism of the former will aid in the understanding of the latter.

For some years, the view was held that hypertension was due to humoral agents. A poor case at best was made for any participation of the nervous system. Indeed, at one time, the nervous system was discarded almost contemptuously; but times have changed. The nervous system now occupies the dominant place, in the opinion of many persons, in maintaining the elevated pressure during the chronic stage. Humoral agents merely initiate the rise during the first few weeks of hypertension, to lose their dominance later. But confusion becomes compounded. Because renin has not been detected with assurance in peripheral blood in increased amounts during the chronic stage of hypertension by the crude methods available, it is assumed that it plays no part in the mechanism. The assumption is made further, on the basis of what seems to me assailable evidence, that the nervous system now takes over the vasoconstrictor function from the humoral. Confronted with this array of inadequate evidence, some resign themselves to the belief that doctors are wholly lacking in insight into the mechanisms of arterial hypertension.

Even the simplest hypertension is a mosaic in which many mechanisms are to a greater or lesser extent involved. Elevated blood pressure is the resultant of multiple forces acting on the variety of tissues which compose the circulatory apparatus. Is it then to be supposed that this is any simple problem the solution of which will be found in the elucidation of but one of these forces?

The various systems chiefly involved in hypertension may be divided, for pedagogic purposes, into groups somewhat as follows:

Clinical	*Experimental*
I. Nervous Participation	
Poliomyelitis of brain stem	Cerebral Ischemia
Porphyria	
Increased intracranial pressure	Cushing's experiment
Sclerosis of carotid sinus	Resection of sinus and aortic depressor nerves
Resection of glossopharyngeal nerve	
Emotion	Hypertension from audiogenic stimulus
Tabes dorsalis	
II. Cardiovascular Participation	
Coarctation of aorta	Clamping of aorta above renal vessels
Heart failure	
Arteriovenous fistula	
Arteriosclerosis	
III. Endocrine Participation	
Hypophysis — basophil adenoma	Anterior lobectomy diminishing blood pressure
Adrenals—pheochromocytoma	Adrenalin hypertension
Cortical carcinoma	Desoxycorticosterone acetate hypertension
Cortical hyperplasia	Bilateral adrenalectomy abolishes hypertension
Thymus—carcinoma with Cushing's syndrome	
Placenta—associated with toxemia of pregnancy	
IV. Renal Participation	
Glomerulonephritis	Antikidney serum nephritis
Obstruction to renal vessels	Mechanical constriction of renal arteries or veins
Pyelonephritis	
Prostatic obstruction	
Polycystic kidneys	Mechanical compression of ureters
Crush syndrome	
Periarteritis nodosa	
Perinephric constriction of the parenchyma	Cellophane or silk perinephritis

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Read in a Symposium on Hypertension in a joint meeting of the Section on Experimental Medicine and the Section on Internal Medicine at the Ninety-Seventh Annual Session of the American Medical Association, Chicago, June 25, 1948.

NEUROGENIC HYPERTENSION

Persistent hypertension of neurogenic origin has been induced in animals by section of the carotid sinus and aortic depressor nerves and by cerebral ischemia resulting from ligation of the blood supply to the brain. Neither method produces hypertension which exactly simulates essential hypertension in human beings; nor could it currently be supposed that the mechanism of the neurogenic component of this disease is faithfully mirrored in these experimentally induced hypertensions. Yet the fact that blood pressure can be persistently elevated by experimental alteration of the nervous system gives hope that the way in which it actually participates may be elucidated.

Koch and Mies [1] were the first to show that sustained hypertension resulted when the carotid sinus and aortic depressor nerves were severed. Subsequent work, chiefly by Heymans,[2] Grimson,[3] Thomas [4] and Bing [5] shows that the hypertension is widely fluctuant, depending on concurrent changes in heart rate. The mechanism of the rise in pressure seems to be a disproportion between the volume content of the arterial tree and its capacity. The disproportion is the result of increased cardiac output due to tachycardia exceeding the peripheral blood flow.

Hypertension due to ligation of cerebral arterial flow of an intermittent sort was produced in dogs by

1. Koch, E., and Mies, H.: Chronischer arterieller Hochdruck durch experimentelle Dauerausschaltung des Blutdruckzügler, Krankheitsforschung **7**: 241, 1929.
2. Heymans, C.: Experimental Arterial Hypertension, New England J. Med. **219**: 147, 1938.
3. Grimson, K. S.: The Sympathetic Nervous System in Neurogenic and Renal Hypertension: Experimental Correlation and Clinical Consideration, Arch. Surg. **43**: 284 (Aug.) 1941.
4. Thomas, C. B., and McLean, R. L.: The Effect of Intravenous Injection of Epinephrin and Angiotonin Before and After the Production of Neurogenic Hypertension, Bull. Johns Hopkins Hosp. **75**: 319, 1944.
5. Bing, R. J.: Hemodynamics of Neurogenic Hypertension, J. Clin. Investigation **23**: 939, 1944.

Nowak and Walker[6] and later by Fishback, Dutra and MacCamy.[7] However, it was so unpredictable and did not occur at all in so many animals, even after severe ischemia, that many observers doubted its existence. Taylor and I repeated this work and found, as had our predecessors, that ligation of the carotid, vertebral and spinal arteries elicited altogether unimpressive elevations of blood pressure (fig. 1).

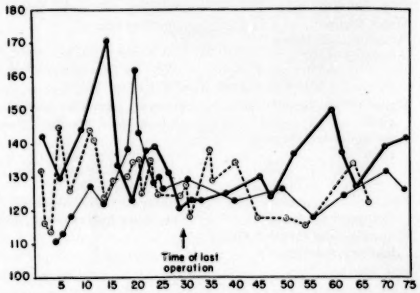

Fig. 1.—The effect on arterial pressure of progressive ligation of vessels to the dog's head. Changes in pressure are irregular despite severe cerebral ischemia. Dog 280 is represented by the heavy line, dog 348 by the light line and dog 424 by the broken line. The horizontal row of figures at the bottom shows the number of days, and the vertical column of figures at the left shows the blood pressure in millimeters of mercury.

We then made a further series of experiments in which all the vessels that could be found going to the head were ligated. These animals usually experienced periodic convulsions and appeared demented, but the elevation in arterial pressure was at least perceptible and often persistent for weeks.

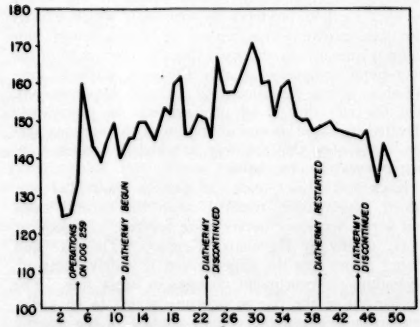

Fig. 2.—The effect of progressive ligation of vessels to the head with daily stimulation by diathermy of a tantalum wire placed just above the obex. Arterial pressure is higher and persists at higher levels for weeks or months. The horizontal row of figures at the bottom shows the time in weeks, and the vertical column of figures shows the blood pressure in millimeters of mercury.

Greater elevation was obtained by implantation of a tantalum wire in the groove of the medulla just above the obex, the exact area being determined by rise in blood pressure at operation following diathermy heating of the wire. The area of the medulla was subjected to daily fifteen minute treatments with inductothermy. Figure 2 shows the more persistent elevation in blood pressure. Discontinuance of treatment was followed by fall in blood pressure to normal or only slightly elevated levels. The injection of kaolin into the ventricular system of the brain was at one time used as a method of producing neurogenic hypertension. Recently, it has been seriously questioned whether anything but brief elevation in blood pressure may be so produced. Our own experience coincides with this. In dogs we have never produced persistent diastolic hypertension by injection of a variety of specimens of kaolin into the cisterna magna. The problem needs further study.

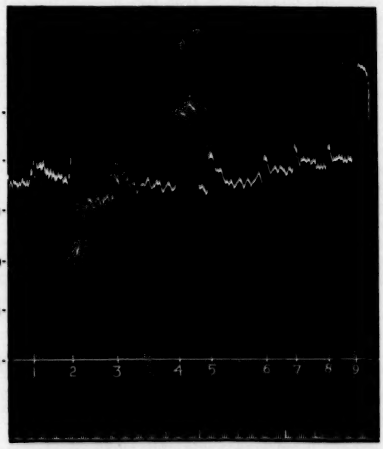

Fig. 3.—Augmentation of angiotonin (144). 1. Angiotonin. 2-3. Tetraethylammonium chloride, 5 mg. per kilogram of body weight. 4. Angiotonin. 5-8. Tetraethylammonium chloride. 9. Angiotonin. This is an example of augmentation that might have significance in the renal hypertensive state.

An interesting method for the production of hypertension in rats tested for their high emotional responsiveness has been developed by Farris, Yeakel and Medoff.[8] In these rats, exposed to the sound of an air blast a minimum of 167 times daily, arterial pressures of from 160 to 180 mm. of mercury developed.

In human beings hypertension often follows bulbar poliomyelitis, chronic porphyria, tabes dorsalis and sclerosis of the carotid sinus. It is strikingly evident in the "hypertensive diencephalic syndrome," along with other evidences of diencephalic hyperactivity. Increased intracranial pressure elevates arterial pressure but not persistently. Disturbance of the psyche is believed by many of the psychiatrically minded to be at the bottom of much hypertension. Probably so, but one must await the proof. Thus, there is much suggestive evidence of nervous system involvement in hypertension, but so far it is lacking in the necessary clarity to be of decisive importance in the objective analysis of the problem in patients.

6. Nowak, S. J. G., and Walker, I. J.: Experimental Studies Concerning the Nature of Hypertension: Their Bearing on Surgical Treatment, New England J. Med. **220**: 269, 1939.

7. Fishback, H. R.; Dutra, F. R., and MacCamy, E. T.: The Production of Chronic Hypertension in Dogs by Progressive Ligation of Arteries Supplying the Head, J. Lab. & Clin. Med. **28**: 1187, 1943.

8. Farris, E. J.; Yeakel, E. H., and Medoff, H. S.: Development of Hypertension in Emotional Gray Norway Rats After Air Blasting, Am. J. Physiol. **144**: 331, 1945.

ENDOCRINE PRODUCTION

Selye[9] and his associates have made an important contribution to inquiry into experimental hypertension. They demonstrated that desoxycorticosterone acetate (D.C.A.) when given to unilaterally nephrectomized female rats, mice or chicks receiving salt in their drinking water, caused severe nephrosclerosis, moderate hypertension and associated vascular changes reminiscent of periarteritis nodosa and rheumatic fever in about three weeks. Monkeys and dogs, even after sixty days of treatment, show only minimal changes. An emulsion of anterior pituitary gland also produces much the same result, presumably because of its stimulating action on the adrenal cortex. But the pituitary and desoxycorticosterone acetate have points of difference, the chief of which being that the action of desoxycorticosterone acetate is unaffected by the protein content of diet, while a 30 per cent casein diet fed after pituitary injection yields 88 per cent of nephrosclerosis as contrasted with 11 per cent on a 15 per cent casein diet. It is possible that the difference in desoxycorticosterone acetate and pituitary action is one of protein metabolism, the former having little or no effect and the latter a profound one. Both desoxycorticosterone acetate and pituitary actions are augmented by sodium chloride. Casein, egg albumin and wheat glutin favor nephrosclerosis, while lactalbumin, gelatin and zein are less effective. Amino acids were ineffective, suggesting that the structural arrangement of a product of protein digestion determines its participation in nephrosclerotic action.

It is not as yet clear why other investigators have not had the same consistent success in reproducing these experiments. All those who have seen the vascular lesions in Selye's rats do not doubt their reality.

In the past years it has become apparent that rare cases of essential hypertension, or what passes for it, seem to originate in a medullary pheochromocytoma. The signs and symptoms of paroxysmal hypertension are not present, and the clinical pattern is that of essential hypertension. The mechanism is obscure, since no one has so far elicited persistent hypertension in animals with epinephrine. Vogt has biologic[10] and Corcoran and I[11] chemical evidence that epinephrine stimulates increased liberation of corticoids. Possibly such a mechanism leads to the production of persistent hypertension in patients with a pheochromocytoma.

The production of hypertension by steroids has its striking clinical counterpart. The hypertension of Cushing's disease or syndrome leaves the physician in little doubt that the adrenal cortex is capable of playing a genetic role in its production.

Of the ovary, little need be said, if only because little is known. The far more direct association of the placenta with pregnancy and the toxemias of pregnancy assumes importance in analysis of the production of hypertension. The time-sanctioned "menopausal hypertension" has not withstood critical experimental analysis. It is with regret my co-workers and I record that it does not exist.[12] There can be little doubt that the endocrine system plays a crucial part in the mechanism of hypertension, but just how it does so is not clear.

CARDIOVASCULAR PRODUCTION

It is by no means certain that there is a special type of diastolic hypertension resulting alone from increased force of the heart beat and/or increased cardiac output. The hypertension of hyperthyroidism is systolic, because of increased cardiac output, and thus does not resemble essential hypertension. Possibly the nearest approach is the hypertension of coarctation of the aorta. If Steele's[13] observation is widely verified, that relative diastolic hypertension exists below the stenosed area as well as above it, it is probable that widespread increase in peripheral resistance has occurred, mediated by nervous or humoral mechanisms or both. The evidence on these points is conflicting and requires more detailed examination before the mechanism will be clear.

My own work merely shows that the aorta of dogs may be clamped off at or near the aortic isthmus without producing significant hypertension proximal to the obstruction.[14] The failure to produce it seems due to the fact that dogs have a remarkable ability to produce collateral circulation. Except for transient weakness in the hind quarters, the animal's blood supply seemed almost unaffected by so drastic a procedure as closing the aorta high in the chest.

RENAL PRODUCTION

A variety of attempts have been made over a period of many years to produce persistent hypertension by operative procedures on the kidneys. These have been associated with the names of such pioneers as Cash, Hartwich, Pässler and Janeway. The results were never wholly satisfying. Probably the best of the methods growing out of this exploration consisted either of reducing the mass of kidney substance by resection of portions of the parenchyma, by ligation of large branches of the main renal artery or by roentgen irradiation of the kidneys transplanted to a position under the skin. These methods had the disadvantage of reducing total renal excretory function, differing thus fundamentally from early essential hypertension in human beings. Goldblatt overcame this disadvantage by the application of constricting clamps on the main renal vessels and so achieved persistent diastolic hypertension without disturbance of renal excretory function. The method has received wide acceptance and has contributed greatly to furtherance of knowledge of experimental hypertension.

The application of cellophane or silk to the parenchyma of the kidneys offers another simple method of producing experimental hypertension. These materials cause irritation with the accumulation of fluid and the ingrowth of fibroblasts. Condensation occurs with the formation of a thick hull around the parenchyma, thus preventing the normal pulsating of the kidneys. Arterial pressure rises slowly over a period of weeks to months without excretory insufficiency.

One other method has been suggested (Dick[15]). Streptococci were injected into the blood stream. The method has not as yet been evaluated by other investigators.

9. Selye, H.: Production of Nephrosclerosis by Overdosage with Desoxycorticosterone Acetate, Canad. M. A. J. **47**: 515, 1942.
10. Vogt, M.: The Output of Cortical Hormone by the Mammalian Suprarenal, J. Physiol. **102**: 341, 1943.
11. Corcoran, A. C., and Page, I. H.: Methods for the Chemical Determination of Corticosteroids in Urine and Plasma, J. Lab. & Clin. Med. **33**: 1326, 1948.
12. Taylor, R. D.; Corcoran, A. C., and Page, I. H.: Menopausal Hypertension: A Critical Study, Am. J. M. Sc. **213**: 475, 1947.
13. Steele, J. M.: Evidence for General Distribution of Peripheral Resistance in Coarctation of the Aorta, J. Clin. Investigation **20**: 473, 1941.
14. Page, I. H.: The Effect of Chronic Constriction of the Aorta on Arterial Blood Pressure in Dogs: An Attempt to Produce Coarctation of the Aorta, Am. Heart J. **19**: 218, 1940.
15. Dick, G. F.: Experimental Hypertension: Its Production in Dogs by Intravenous Injection of Streptococci, Arch. Path. **39**: 81 (Jan.) 1945.

Selye [16] produced hypertension by placing a ligature around the aorta at a level between the two renal arteries sufficiently tightly drawn to reduce the pressure below it to a level at which, although blood flow continues, glomerular filtration can no longer occur. Life is maintained by the renal tissue above the tie. Extensive vascular damage occurs, killing the animal within weeks or months. The normal morphologic pattern of the kidney is replaced by aggregates of large cells apparently arising from the epithelium of the lower third of the proximal tubule. The tissue resembles that of adrenal cortex. Selye stated the belief that these cells are the source of renin.

A disturbing note has crept into current theory recently. The position has been vigorously maintained by Goldblatt and Houssay for some years that removal of both kidneys was not associated with rise in blood pressure, despite the observation of Jeffers, Lindauer, Twaddle and Wolferth [17] and Grollman and Rule [18] that the removal of three of the four kidneys in parabiotic rats resulted in hypertension in the nephrectomized animal. In 1947 Braun-Menendez and v. Euler [19] reported that a rise of pressure occurred in only 3 of 23 such pairs. They then joined 3 rats in parabiosis, one bilaterally nephrectomized animal between 2 normal animals. Definite hypertension occurred in all 6 trios. Further, they found that one third of nephrectomized rats showed hypertension usually during the second or third day after nephrectomy. These interesting observations have not been explained.

Every one now recognizes that the obvious clinical counterparts of experimental renal hypertension are rare. Occasional patients with arteriosclerotic obstruction of the renal arteries, perinephric hulls, Wilm's tumors compressing the renal parenchyma and the like are seen, but the average hypertensive patient has none of these. Is there, then, any evident similarity between the kidney in the human hypertension and that in the experimental form? It has seemed to Corcoran and me that the interstitial fibrosis of the pyelonephritic kidney might mimic the cellophane perinephric hull by reducing the pulsation of the kidneys. But in early hypertension the changes in kidneys, if any, have eluded us all. Because of the pronounced somatic expression of nervous overactivity in some patients, the opinion exists that in some unknown manner the kidneys are stimulated to produce pressor substances. Kottke, Kubicek and Visscher's [20] experiments on stimulation of the renal nerves suggest that hypertension occurs only as long as the nerves are being stimulated. That any such mechanism exists in patients is pure conjecture.

MECHANISMS OF RENAL HYPERTENSION

Experimental renal hypertension more closely simulates essential hypertension in human beings than any other experimental form. This is good reason for its having been more extensively studied than others. A danger lurks in the use of the term "renal," because of the implication that the kidneys alone supply the mechanism for elevation of arterial pressure to abnormal heights. While the kidneys may be accorded primacy in some, they could not produce hypertension without active participation of the circulation with its multiple controls.

Hypertension can be produced either by severing the carotid sinus and aortic depressor nerves or by producing cerebral ischemia along with medullary stimulation. The hemodynamic changes in neither are identical with those in the usual patient with essential hypertension, although certain similarities exist. For example, arterial pressure is in large measure determined by heart rate in both animals after sinoaortic nerve section just as it is in some patients with early essential hypertension. However, the differences rather than the similarities are at present the more evident.

NERVOUS PARTICIPATION

The part played by the renal nerves has of late caused some interest and indeed some concern. Observations made in both hypertensive patients and dogs showed no special participation of these nerves in the mechanism of renal hypertension. Kottke, Kubicek, and Visscher [20] found persistent hypertension in dogs as long as the renal nerves were stimulated continuously by indwelling electrodes. Every one hoped that the hypertension would persist after discontinuation of the stimulation, but it did not. Even more recently, Trueta [21] made the interesting, if somewhat imaginative, claim that hypertension is due to shunting of blood through juxtamedullary glomeruli via sluiceways more directly into the venous system, so eliciting cortical ischemia. This shunting seems to be under nervous control. Strongly against this notion is the fact that Bradley [22] found normal extraction percentages in the kidneys of hypertensive patients. Further, there is no substantial current evidence indicating that cortical ischemia is in itself a cause of hypertension.

Thus, in animals with experimental renal hypertension, severing the renal nerves neither lowers blood pressure nor prevents elicitation of hypertension. Splanchnic nerve section, anterior nerve root section and even "total" sympathectomy with cardiac denervation are all without decisive influence on the elevated blood pressure. Destruction of the cord leads to profound fall in blood pressure, but, if the animals can be kept in a fair state of health, hypertension returns, but not to its preoperative level. Whatever the mechanism, destruction of the cord affects blood pressure significantly, while sympathectomy does not, in animals with renal hypertension. Here, there is both a similarity to and difference from patients with hypertension. It is not clear what function the pressor substances found in the cerebrospinal fluid have in the genesis of neurogenic hypertension. I [23] found such a substance in 1937 and Raab [24] more recently. Raab reviewed admirably the nature of this problem.

ENDOCRINE PARTICIPATION

Systematic experiment shows that the removal of the entire pituitary gland in both rats and dogs is associated with fall in blood pressure, but usually not to

16. Selye, H.: Transformation of the Kidney into an Exclusively Endocrine Organ, Nature, London **158**: 131, 1946.
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18. Grollman, A., and Rule, C.: Experimentally Induced Hypertension in Parabiotic Rats, Am. J. Physiol. **138**: 587, 1942.
19. Braun-Menendez, E., and von Euler, C. S.: Hypertension After Bilateral Nephrectomy in the Rat, Nature, London **160**: 905, 1947.
20. Kottke, F. J.; Kubicek, W. G., and Visscher, M. B.: The Production of Arterial Hypertension by Chronic Renal Artery—Nerve Stimulation, Am. J. Physiol. **145**: 38, 1945.
21. Trueta, J.; Barclay, A. E.; Daniel, P. M.; Franklin, K. J., and Prichard, M. M. L.: Studies of the Renal Circulation, Springfield, Ill., Charles C Thomas, Publisher, 1947.
22. Bradley, S.: The Validity of the Clearance Technique in the Measurement of Renal Blood Flow in Normal Man and in Patients with Essential Hypertension, in Zweifah, B. W., and Shorr, E.: Factors Regulating Blood Pressure, New York, Josiah Macy Jr. Foundation, 1947.
23. Page, I. H.: A Highly Active Pressor Substance from Cerebral Ventricular Fluid of Human Beings, Science **82**: 550, 1935.
24. Raab, W.: Adreno-Sympathogenic Heart Disease (Neurohumoral Factors in Pathogenesis and Treatment), Ann. Int. Med. **28**: 1010, 1948.

wholly normal levels. The fall is slow, suggesting an indirect rather than direct participation in the mechanism controlling blood pressure. Removal of the postpituitary has no effect, while loss of the anterior reproduces completely the arterial pressure changes of total hypophysectomy. After the fall in blood pressure, according to the careful work of Anderson, Page, Li and Ogden,[25] it may be again raised to the original hypertensive level by administration of the pure adrenocorticotrophic hormone of Li and Evans.

The view that the adrenal glands are more directly concerned in the mechanism of hypertension comes from the early observations on experimental renal hypertension that removal of both glands causes a fall in arterial pressure to normal or even below. Administration of salt is insufficient treatment to restore the hypertension. Lewis and I have studied the effect of a variety of other treatments. Compound A acetate plus desoxycorticosterone acetate kept the blood pressure at a level as great as or greater than before adrenalectomy. Desoxycorticosterone acetate alone over an extended period led to severe attacks of hypoglycemia, but arterial pressure tended to remain elevated in the salt-fed animals.

Studies of Gaudino [26] suggest that the fall in blood pressure, in rats at least, is associated with reduction of renin substrate in the blood. This is the protein substrate on which renin acts to produce angiotonin. In normal rats, bilateral adrenalectomy produces a sharp fall together with some reduction of blood pressure. In only 5 of the 10 hypertensive rats did substrate fall, despite reduction to normal in arterial pressure. Treatment of the adrenalectomized normal rats with desoxycorticosterone acetate restored the renin substrate to normal concentrations and arterial pressure to normal. Similar treatment of the hypertensive adrenalectomized rats reestablished the hypertension. No measurements of the substrate appear to have been made in the latter group.

Lewis and Goldblatt [27] claimed to have demonstrated complete disappearance of substrate in the blood of untreated adrenalectomized dogs. Adequate therapy with adrenal cortical hormones or desoxycorticosterone acetate resulted in a return to normal level. Full details of these experiments reported in 1942 as yet have not appeared.

This explanation of the mechanism of adrenal participation in hypertension is attractive indeed, but closer scrutiny of the results so far published is not encouraging. The method for the determination of substrate is crude in the extreme, and the results with hypertensive rats shows only one half of them exhibiting a fall in substrate while all show a fall in pressure.

Finally, the observation that desoxycorticosterone acetate acts on the metabolism of a protein is entirely foreign to what is known of this substance. There is good evidence to show that desoxycorticosterone acetate is without action on protein synthesis. That it should act alone on renin substrate is unlikely. Therefore, until more and better evidence is available, it seems necessary to suspend judgment on the Lewis and Goldblatt and Gaudino evidence as providing the solution to the vital problem of how the adrenal glands participate in the mechanism of hypertension.

Since Selye was able to produce nephrosclerosis and hypertension by administration of anterior pituitary or desoxycorticosterone acetate, it is natural to suppose a similar mechanism in human hypertension. Desoxycorticosterone acetate occurs in minute amounts in the normal human adrenal cortex. Even this small amount present over long periods of time might produce vascular change. There are obviously many other possibilities for participation in the mechanism of hypertension by both pituitary and cortical steroids. At present, there is no evidence on which to form any opinion as to the probability of any of them.

Perera [28] described the occurrence of Addison's disease in a patient with essential hypertension which throws some light on adrenal participation in the latter. While the patient was receiving desoxycorticosterone acetate, the pressure was persistently elevated. Replacement therapy with salt alone, even though the patient was in electrolyte and water equilibrium, resulted in a drop of blood pressure to normal. The results parallel those described previously for animals with experimental hypertension. Rigid restriction of sodium chloride from the diet in patients obliterates the pressor action of desoxycorticosterone acetate which follows its injection into those receiving salt. Hypertensive persons seem to be more susceptible to desoxycorticosterone acetate than normal persons, because the twice daily injections of 5 mg. produce a rise in both systolic and diastolic pressures in the former but not in the latter. The rise could not be attributed to salt and water retention alone, since comparable retention occurred in normotensive persons (Perera and Blood [29]).

HUMORAL PARTICIPATION

Contemporary thinking on humoral participation in the mechanism of renal hypertension exhibits dichotomy. Some believe that, as the result of changes in the character of the blood flow within the kidneys, renin is liberated from the tubular cells to react with renin substrate to produce angiotonin or a protein-bound prototype. Others think that hypertension is the result of ischemia of the kidneys of a degree sufficient to provoke the production of pressor amines, of which hydroxytyramine is the prototype. Holding to the former opinion, I shall emphasize that view.

As Corcoran and I [30] showed in dogs made hypertensive by clamps on the renal arteries or by cellophane perinephritis, hypertension could be produced without more than transient reduction of renal blood flow. In patients with essential hypertension, Goldring and Chasis [31] found reduction of blood flow only late in the course of the disease, not during its initiation, a fact we have repeatedly confirmed (Corcoran, Taylor and Page [32]). It is hard, therefore, to understand how hypoxia of sufficient degree could occur to set in motion the enzymatic degradation of amino acids to pressor

25. Anderson, E.; Page, E. W.; Li, C. H., and Ogden, E.: Restoration of Renal Hypertension in Hypophysectomized Rats by the Administration of Adrenocorticotrophic Hormone, Am. J. Physiol. **141**: 393, 1944.

26. Gaudino, N. M.: Accion de las Glandulas Suprarrenales Sobre el Hipertensinogeno, Rev. de la Soc. Argent. de Biol. **20**: 529, 1944. Las Suprarrenales en la Hipertension Arterial Nefrogena, Rev. Soc. Argent. de biol. **20**: 470, 1944.

27. Lewis, H. A., and Goldblatt, H.: Studies on Experimental Hypertension: XVIII. Experimental Observations on the Humoral Mechanism of Hypertension, Bull. New York Acad. Med. **18**: 459, 1942.

28. Perera, G. A.: The Relationship of the Adrenal Cortex to Hypertension, J. A. M. A. **129**: 537 (Oct. 20) 1945.

29. Perera, G. A., and Blood, D. W.: The Relationships of Sodium Chloride to Hypertension, J. Clin. Investigation **26**: 1109, 1947. Pressor Activity of Desoxycorticosterone Acetate in Normotensive and Hypertensive Subjects, Ann. Int. Med. **27**: 401, 1947.

30. Corcoran, A. C., and Page, I. H.: Renal Blood Flow in Experimental Renal Hypertension, Am. J. Physiol. **135**: 361, 1942.

31. Goldring, W., and Chasis, H.: Hypertension and Hypertensive Disease, New York, The Commonwealth Fund, 1944.

32. Corcoran, A. C.; Taylor, R. D., and Page, I. H.: Functional Patterns in Renal Disease, Ann. Int. Med. **28**: 560, 1948.

amines and suppress the destructive action of the amine oxidases.

The renal vasopressor system, made up as it is of renin, renin substrate and angiotonin, seems to me the one more likely to be concerned in the genesis of experimental renal hypertension. Renin is a proteolytic enzyme contained in the tubular cells which acts on an α_2 globulin produced by the liver and contained in the blood. The product of the reaction is angiotonin (hypertensin), a polypeptide which is highly pressor in its action. It is possible that in the body angiotonin is combined with protein and is split off only by such treatment as precipitation with alcohol or heat to produce the angiotonin as it is known at present. Aside from conjecture, there are two bits of evidence which suggest this possibility. Some years ago, my co-workers and I found a protein-like vasoconstrictor substance in the blood of hypertensive and normal patients and dogs as demonstrated on the rabbit's ear vessels perfused with plasma. The possibility of the presence of a vasoconstrictor substance resulting from coagulation of the blood prevented us from being certain of our results. The problem is again under active investigation, now that Rapport, Green and I [33] have found a method of inactivating the serum vasoconstrictor (crystalline "serotonin").

The second bit of evidence is more convincing and comes from the work of our former colleagues Helmer, Shipley and Kohlstaedt.[34] They found that plasma from sick or shocked animals, or ones given injections of crude extracts of kidney, contains a pressor substance which when injected into nephrectomized cats produces a sustained rise in blood pressure. The material was partially purified by ammonium sulfate precipitation. Its nature is not as yet elucidated. Whether such a substance occurs in hypertension is not known, and its study will be awaited with keen interest.

A further dichotomy of thought has occurred, largely, I suppose, because of the difficulty of finding sufficient quantities of renin in peripheral blood to account for the rise in blood pressure. Thus Ogden [35] has marshalled the evidence in a stimulating fashion to suggest that during the first weeks of experimental renal hypertension the humoral mechanism is chiefly responsible, displaced later by the vasoconstrictor action of the nervous system. Another view reverses this sequence, giving primacy to the nervous mechanism, the humoral prevailing later. The evidence for either view is not strong.

One must recognize, as Leloir, Munoz, Taquini, Braun-Menendez and Fasciolo [36] originally showed, that shocking operations cause the immediate liberation of renin into the blood stream, and therefore it is not surprising that the enzyme should be found in excess in peripheral blood after operation on the kidneys to induce hypertension. As we have seen, renin itself is not a vasoactive substance; it is merely one component of a complex system yielding vasopressor substance. Its measurement out of the framework in which it works, i.e., the highly artificial in vitro environment, has to me only limited significance. Could the effector substance itself be measured, whatever it be, the results would be far more apposite. As has been repeatedly emphasized, the physiologic mechanisms of hypertension are multiple and interconnected. Just so are the chemical ones. Their simplification on the basis of ignorance of their complexity can lead only to premature apostasy.

Thus renin appears early in the blood after operation on the kidneys, and from this it is argued that the hypertension is initiated by the renal vasopressor system. After a week or so, renin disappears from the blood as measured by contemporary methods, hence, the argument runs, nervous control has taken over. The argument exemplifies the complexities of humoral control and the inadequacy of present evidence to offer satisfying answers to the problem of its participation in the regulation of blood pressure.

Most of the known pressor agents as causes for hypertension are ruled out by their pharmacologic properties. For example, many elevate arterial pressure by increasing cardiac output, a phenomenon not consonant with the hemodynamics of essential or experimental renal hypertension. Many of them produce severe symptoms, again not in accordance with observations on early essential hypertension. For these and other cogent reasons, angiotonin seems from the testimony of brief experiments in both human beings and animals most nearly to reproduce the mechanism which elevates arterial pressure. Yet the reproduction is not sufficiently perfect to be certain that it, in its present form, is the one solely involved.

This is a highly complex problem which will find no easy solution. Yet let no one doubt that methods are not now at hand for its solution. It is not for lack of knowledge that one must wait; it is for lack of hands and heads with which to do it.

THE VASCULAR SUBSTRATE

Investigation of the factors which control the responsiveness of the blood vessels to stimuli has not progressed to the point clarifying the problem of the state of the vessels in hypertension. Actually, only a vague directional trend is in the process of being established—one of great physiologic interest, but one not yet shown to be apposite to the hypertensive state.

With Taylor and Reinhard,[37] I have studied this problem for several years, it being our special concern during the war years because of its applicability to the problem of shock. Animals and man in deep shock show greatly reduced pressor and depressor responses to chemical stimuli such as epinephrine and angiotonin. Supposedly normal, anesthetized animals exhibit widely differing responses from day to day and even during the same experiment. Significant average responses were obtainable only after study of large numbers of animals. Thus, the blood vessels or the stimuli or both must be highly variant.

The nervous system plays an important part in the control of vascular responsiveness. Injury to it temporarily reduces responsiveness, while its rapid complete destruction enhances responsiveness. Thus section of the cord at the sixth cervical segment and destruction caudad yield a preparation that for days or weeks is highly sensitive to vasoactive substances. It is made much more sensitive by denervation of the carotid sinus and vagotomy. Administration of tetraethylam-

33. Rapport, M. M.; Green, A. A., and Page, I. H.: The Enzymatic Inactivation of Serum Vasoconstrictor, Proc. Soc. Exp. Biol. and Med. **68**: 582, 1948.

34. Helmer, O. M.; Shipley, R. E., and Kohlstaedt, K. G.: Nature of a Principle in Blood Which Elicits a Sustained Pressor Response in Nephrectomized Animals, Federation Proc. **6**: 128, 1947.

35. Ogden, E.: The Extra-Renal Sequel to Experimental Renal Hypertension, Bull. New York Acad. Med. **23**: 643, 1947.

36. Leloir, L. F.; Munoz, J. M.; Taquini, A. C.; Braun-Menendez, E., and Fasciolo, J. C.: La formacion del hipertensinogeno, Rev. argent. de cardiol. **9**: 269, 1942.

37. (*a*) Page, I. H., and Taylor, R. D.: Mechanism of Renal Tachyphylaxis: Restoration of Responsiveness by Tetraethyl Ammonium Ion, Science **105**: 622, 1947. (*b*) Page, I. H.: Some Humoral Factors in Hypertension, in Zweifah, B. W., and Shorr, E.: Factors Regulating Blood Pressure, New York, Josiah Macy Jr. Foundation, 1947.

monium chloride (T.E.A.) usually further enhances the responsiveness, but only slightly. The sympathetic nervous system appears thus to be acting in a strongly inhibitory sense rather than the more usual augmentative role.

As Acheson and Moe [38] have shown, tetraethylammonium chloride produces its effect chiefly by blocking transmission through autonomic ganglions. The result of this demonstration has been the wide use of tetraethylammonium chloride as a diagnostic and therapeutic agent in clinical medicine, especially by Lyons, Moe and Hoobler and their groups.

Our interest began when we found that administration of large doses of the drug greatly augmented the vascular responsiveness to a variety of vasoactive substances, such as angiotonin, barium chloride, epinephrine and arterenol® (3,4-dihydroxyphenylethanolamine), and that in certain circumstances the lost responsiveness caused by repeated injections of renin was restored.[37b] I would agree with Moe that the most probable explanation of this truly remarkable action is based on release of all inhibitory nerve impulses.

As it concerns hypertension, the fact emerges that normal animals are converted by repeated doses of tetraethylammonium chloride from "depressor" preparations to "pressor" ones in which the pressure rises instead of falling when tetraethylammonium chloride is given. The first dose of tetraethylammonium chloride gives a large fall, but on repetition less and less occurs until nothing but pronounced rises occurs. Part of the rise is probably due to adrenal stimulation as Acheson and Moe suggest, for as large pressor responses in adrenalectomized dogs were not observed. Destruction of the spinal cord itself is sufficient to insure only pressor responses. If the adrenal glands are removed from such animals, a pressor response is still obtained. Such animals are so exquisitely responsive to pressor stimuli that they remind one of the beginning phase of hypertension in some patients. Removal of both kidneys still further increases responsiveness, especially to renin and angiotonin. The effect is not immediate, however, a day at least being required, suggesting the possibility that a sensitizing agent is being retained or not destroyed, the prototype of which well may be the tetraethylammonium ion.

Removal of the liver, in contrast, greatly depresses vascular responsiveness. Despite the fact that arterial pressure may be temporarily well maintained, the response to a variety of agents is damped. For reasons not at all clear, tetraethylammonium chloride does not exert its augmenting action in any significant degree in these hepatectomized animals.

With only these crude facts at one's command, it is possible greatly to depress or abolish responsiveness or greatly to heighten it. If such factors participate significantly in the hypertensive patient, and surely they may, the amount of a pressor substance or nerve stimulus required to elevate arterial pressure would be irrevocably tied to the responsiveness of the vascular tree. Lacking the latter datum, even the accurate estimates of the amounts of pressor agents lose significance to an alarming degree.

Several years ago my co-workers and I found that plasma of hypertensive dogs exhibited greater than normal vasoconstrictive power when perfused with plasma through rabbit's ear vessels. As we pointed out, the amount was in no way proportional to the height of the blood pressure. Further, the results are complicated by the presence of the vasoconstrictor which forms when blood clots. Thus any method in which pressor agents are sought in blood is subject to an incredibly large number of pitfalls. It is only recently that we have begun to appreciate the complexity of the depressor-pressor systems of the blood and to overcome the naiveté of our approach a decade or more ago. Whatever the assurance of our colleagues, our view has turned to one of humility before the complex equilibria of vasoactive substances in the blood and their interaction with the changing reactivity of the blood vessel substrate on which they act. The kidney is only one part of this relationship and, though of great importance, should not be given primacy to the exclusion of other controlling factors.

To return to the problem of vasoconstrictor in the hypertensive patient's blood, Solandt, Nassim and Cowan [39] found greater rises in arterial pressure when hypertensive dog's blood was cross transfused than when a normotensive dog's blood was used. In patients, according especially to Prinzmetal, this is not the case. Taylor, Prince and I have studied this problem recently. We found no difference between hypertensive and normal dogs on cross circulation. A non-epinephrine-like substance appears in the blood, especially in hypertensive dogs but by no means limited to them. The irregularity of its occurrence has doubtless contributed greatly to the current confusion. One must therefore await further evidence.

When the kidneys of dogs with long-standing hypertension were removed, the blood pressure did not return to normal as had been shown by Pickering [40] and others. Further, we found that the plasma retained its vasoconstrictor properties until the death of the animal. This, in conjunction with the fact that the blood vessels in such circumstances became more sensitive to vasoactive humoral agents, might possibly explain persistence of the hypertension. Indeed, some of the animals became so sensitive that normal amounts of pressor agents might have accounted for hypertension.

CONCLUSION

To those not deeply imbued with the sense of urgent need for the solution of the problem of hypertension, many of these studies must seem trivial or inadequate. So much so that to some the endeavor hardly seems worth pursuing. To the optimist, the price of success is trouble. That there is plenty of the latter all could agree. Whether their resolution will lead to success remains for the future to decide.

ABSTRACT OF DISCUSSION

DR. CARLOS JIMENEZ DIAZ, Madrid, Spain: My co-workers and I are studying the mechanisms of regulation of the stimuli causing hypertension. We have utilized the pressor effect of electric stimulation of the central end of the cut vagi. This effect is visible even after the hypophysis has been removed and also after a bilateral nephrectomy and adrenalectomy, but disappears when the cord is sectioned. One must accept that the stimuli pass to the nervous centers and descend to the vascular innervation by the spinal cord and sympathetic fibers. In a second series of experiments on crossed blood circulation we found that excitation in donor dogs produces a hypertensive answer in the receptor. We assume that the nervous action

38. Acheson, G. H., and Moe, G. K.: The Action of Tetraethylammonium Ion on the Mammalian Circulation, J. Pharmacol. & Exper. Therap. **87**: 220, 1946.

39. Solandt, D. Y.; Nassim, R., and Cowan, C. R.: Hypertensive Effect of Blood from Hypertensive Dogs, Lancet **1**: 873, 1940.

40. Pickering, G. W.: The Role of the Kidney in Acute and Chronic Hypertension Following Renal Artery Constriction in the Rabbit, Clin. Sc. **5**: 229, 1945.

on the arterial wall elicits the production of a chemical tonogenic substance. We have made also experiments on a divided dog, in which the superior and inferior parts of the dog's body are connected only by the spinal cord. Circulation of the superior part is maintained by his own heart, and the inferior is perfused by a pump. As we excite the vagi we increase the blood pressure not only in the superior but also in the inferior perfused part. The most interesting observation is that if we perfuse not with dog's plasma as in the earlier experiment but with saline serum the stimulation does not produce hypertension in the inferior part of the dog's body. The inference is: (1) that nervous action on blood pressure is initiated by the production of a pressor substance and (2) that these substances arise from the action of some secretion of the arterial wall on a preexisting substance in the blood plasma. Indeed we have prepared extracts of arterial wall, and we made incubation with the plasma's renin-substrate; the results are clear and constant: extractions of arterial wall are without effect, and when incubated with plasma the pressor effect is exactly the same as with renin plus renin-substrate. These experiments can bring new understanding of the problem of hypertension and indicate the main part that, in the regulation of blood pressure, in addition to other factors, a true internal secretion of the artery may play. It is possible that arterial hypertension, as other constitutional diseases, can be considered in the future as a variation in activity of enzymatic systems.

LOW SODIUM CHLORIDE DIETS IN HYPERTENSION

Effects on Blood Pressure

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The present study was made in an attempt to evaluate the effects of restriction of dietary sodium chloride on the blood pressure of hypertensive patients. For many years, diets low in sodium chloride (salt) have been advocated as a rational measure in the treatment of arterial hypertension. Their use, however, has not been altogether accepted, although in occasional patients striking reductions in blood pressure have been reported.[1] A critical evaluation therefore seemed necessary under as controlled conditions as possible, with the effects of hospitalization, bed rest, sedation and psychotherapeutic influences eliminated so far as practicable.[2] In planning our previous study [2] and the observations reported herein, we have selected low salt regimens which can be observed by a patient at home with relative ease.

During the course of this study, it soon became evident that beneficial results on the level of blood pressure did not occur in most hypertensive patients when other factors were controlled. This was in accordance with the past experience of one of us (H. A. S.). On the other hand, it also became apparent that some patients were benefited insofar as their blood pressures were concerned by the restriction of salt, and it appeared important to attempt to differentiate the group favorably affected from that not affected. Since it was suspected from clinical observations that patients who would respond to the restriction of salt in their diets had certain characteristics in common, some patients were selected for this study because they exhibited these peculiarities. Therefore, the results here reported can in no way be examined statistically, as they involve a larger proportion of subjects whose blood pressures were influenced by salt restriction than would be found in the general hypertensive population.

METHODS OF OBSERVATION

Twenty-two patients were selected for study and admitted to a metabolic ward. In most instances, no changes in regimen were made for two to six weeks, in order that the blood pressures could be measured under controlled conditions. Measurements were made in the morning before arising and in the afternoon after half an hour of bed rest. The averages shown in table 1 were made from all readings during seven to ten days at the end of the control period and at the end of the period of restriction of salt. Most patients were ambulatory on the ward; a few remained in bed, but this factor was constant throughout the experiment. Diets consisted of the usual hospital menu, but a few patients ingested diets restricted as to salt during the control period with salt added in the form of capsules. Patients were not led to believe that the restriction of salt would be in any way beneficial, nor were they informed of the levels of their blood pressures.

The amount of sodium in the diet was calculated from standard tables [3] and was expressed as sodium chloride. In 7 cases a diet composed of rice and fruit juices was used (Kempner diet [4]); in the others, protein was restricted only so far as was made necessary by salt restriction. Lately salt-poor milk (lonolac,® Mead Johnson and Company) was used to increase the protein intake. Sodium chloride in the diet was restricted to 0.5 Gm. per day in 9 cases, to 1.0 Gm. in 12 and to 2.0 Gm. in 3.

RESULTS

Effects of Sodium Chloride Restriction on Blood Pressure.—In 13 of 22 cases, changes in average diastolic blood pressure of 9 mm. of mercury or less were observed after restriction of dietary salt (table 1). In 3 of these cases, the systolic blood pressure fell from 21 to 25 mm. of mercury and in 1 other, 15 mm. of mercury. No other effect on the progress of the disease was noted which could not be explained on the basis of rest and hospitalization. The conditions of 3 became worse. One (case 3), with poor renal function, died, probably as a result of salt deficiency initiated by the diet. In 1 (case 11), the clearance of urea fell from 33 to 15 per cent of normal and in another (case 9) fresh hemorrhages appeared in the eyegrounds. Six of the patients received diets containing 0.5 Gm. of sodium chloride, 5 received 1 Gm. and 3 received 2 Gm.

In 9 cases, the average diastolic blood pressure fell from 14 to 36 mm. of mercury, reaching levels below 100 mm. in 6 and below 90 mm. in 2. The systolic pressure likewise fell from 60 to 19 mm. of mercury (table 1). In most of these cases, symptomatic improvement occurred. Otherwise, changes in the status of the disease were not evident. Three of the 9 received diets containing 0.5 Gm. of sodium chloride,

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1. For a review and bibliography of this subject, the reader is referred to Schroeder, H. A.: Low Salt Diets and Hypertension, Am. J. Med. **4**: 578-587, 1948.

2. Details of this study, case histories of 12 of the patients studied and charts showing the variations in blood pressure of 9 have been published: Schroeder, H. A.; Futcher, P. H., and Goldman, M. L.: The Effects of the "Rice Diet" upon the Blood Pressure of Hypertensive Individuals, Ann. Int. Med. **30**: 713-732, 1949.

3. Sherman, H. C.: Chemistry of Food and Nutrition, ed. 6, New York, The Macmillan Company, 1941.

4. Kempner, W.: Treatment of Hypertensive Vascular Disease with Rice Diet, Am. J. Med. **4**: 545-577, 1948.

and 6 received 1.0 Gm. On the whole, this group represented patients in less severe stages, 7 of them exhibiting minimum changes in their ocular fundi and all manifesting good renal function. The diastolic pressures of only 4 were 115 mm. of mercury or more at the end of the control period, while of the group which did not respond, all but 2 had diastolic pressures at this level or above.

Analysis of Patients Responding to Restriction of Salt.—Those patients who responded by a significant fall in blood pressure to restriction of salt were mon to many and were not present in other cases. In addition, the response of their blood pressures to salt restriction usually occurred in a matter of a few days, and when salt was added to their diets, as in 4 cases, blood pressures became definitely elevated to or nearly to the control values.

The 6 patients in question were all women and all obese. They sometimes gave a history of obesity appearing comparatively rapidly, at puberty or after childbirth. Characteristic of these patients was the difficulty they experienced in attempting to lose weight.

TABLE 1.—*Response of Blood Pressure to Dietary Restriction of Sodium Chloride*

Case No.	Patient	Sex	Age, Yr.	Duration Yr.*	Average Blood Pressure at End of Control Period, Mm. Hg.†	Sodium Chloride in Diet, Gm.	No. Days on Diet	Average Blood Pressure at End of Dietary Period, Mm. Hg.†	Change, Mm. Hg.	Renal Function‡	Ocular Fundi, Grade	Comment
						Poor Response						
1	S. T.	♀§	35	15	235/120	1.0	56	210/118	−15/− 2	Excellent	II	General obesity
2	P. S.	♀§	30	6	204/128	1.0	40	208/127	+ 4/− 1	Good	I	Bilateral slight hydronephrosis; large neurogenic element
3	S. K.	♀	56	4	232/119	0.5‖	16	224/119	− 8/ 0	Poor	III	Died; uremia from sodium chloride deficiency
4	V. R.	♀	41	10	168/113	1.0	44	169/110	+ 1/− 3	Good	I	Large neurogenic element
5	F. W.	♀	23	1	183/115	1.0	50	162/118	−21/+ 3	Fair	II	Large neurogenic element
6	K. E.	♀	30	2¶	187/126	0.5	10	189/129	+ 2/+ 3	Fair	II	Left hemiplegia
7	D. R.	♀	30	6	217/150	2.0	10	213/155	− 4/+ 5	Uremic	III	Chronic glomerulonephritis
8	P. R.	♂	53	30	175/100	2.0	12	166/ 92	− 9/− 8	Uremic	III	Chronic pyelonephritis
9	A. K.	♂	43	1¶	204/119	0.5‖	21	197/113	− 7/− 6	Fair	III	Early malignant stage; no response to sympathectomy #
10	L. M.	♂	36	4¶	198/134	0.5‖	25	177/128	−21/− 6	Good	II	No response to sympathectomy #
11	A. P.	♂	42	1¶	256/160	1.0	30	251/163	− 5/+ 3	Poor	IV	Malignant stage
					251/163	0.5‖	90	226/162	−25/− 1	Poor	III	
12	A. B.	♂	44	10	222/159	0.5	21	209/150	−11/− 9	Good	IV	Malignant stage
13	T. A.	♂	32	3¶	205/140	2.0	13	201/150	− 4/+10	Poor	II	Effect of bed rest not controlled
						Significant Response						
14	A. F.	♂	39	1	168/112	0.5‖	35	137/ 93	−31/−19	Excellent	0	Renal calculus, mild hypertension, blood pressure was not elevated by addition of 12 Gm. sodium chloride to diet
15	W. D.	♂	43	2¶	195/132	1.0	31	163/109	−32/−23	Good	I	Moderate neurogenic element
16	C. O.	♀	38	22	156/107	0.5‖	21	126/ 93	−30/−14	Good	I	Hirsutism without obesity; large neurogenic element; blood pressure elevated when 8 Gm. of sodium chloride added to diet
17	L. S.	♀	42	11	191/108	0.5‖	31	160/ 88	−22/−20	Good	I	Obesity of trunk and face; blood pressure returned to previous level when 6 Gm. sodium chloride added to diet
18	L. C.	♀	33	7¶	199/123	1.0	21	167/106	−32/−17	Good	I	Pronounced obesity of trunk and face; hirsutism; blood pressure elevated when 8 Gm. sodium chloride added to diet
					190/119	1.0	24	164/109	−26/−10			
19	I. H.	♀	40	11	161/110	1.0	21	137/ 92	−24/−18	Good	I	Obesity of trunk and face; blood pressure elevated when 10 Gm. sodium chloride added to diet
20	M. P.	♀	43	6	220/131	1.0	15	140/ 95	−60/−36	Good	I	Effect of bed rest not controlled; obesity of trunk and face
21	M. L.	♀	45	1½	176/119	1.0	28	157/104	−19/−15	Excellent	III	Obesity of trunk and face; decided elevation of blood pressure with 10 mg. desoxycorticosterone acetate daily
22	F. R.	♀§	48	2	185/ 97	1.0	50	127/ 77	−58/−20	Good	II	Obesity of trunk and face; striae; effect of bed rest not controlled

* Duration of hypertension.
† Average blood pressure for the last seven to ten days of the period of observation.
‡ Excellent—normal concentrating ability of kidneys and normal urea clearance; good—slight impairment of concentrating ability with normal urea clearance; fair—impairment of concentrating ability and subnormal urea clearance; poor—urea clearance below 50 per cent of normal without nitrogen retention; uremic—nitrogen retention in blood.
§ Studied in the Hospital of the Rockefeller Institute. ¶ Unknown duration, more than figure shown. ‖ Rice diet (Kempner).
# Lumbodorsal.

examined in an attempt to determine the presence or absence of common characteristics, or of differences from those who did not respond. Of the 9 favorably affected, 2 (cases 14 and 16) were in milder stages of the disease, one of them being a highly suggestible psychoneurotic person. One (case 15) appeared to be affected only after a relatively prolonged period (three weeks) on the diet, and in 1 (case 14) the later addition of salt had no unfavorable effect. It is uncertain, therefore, that salt restriction alone produced the changes observed. The other 6 appeared to belong to a definite but not completely defined group in that certain clinical and laboratory observations were common to many and were not present in other cases. Their histories appeared to attest the ineffectiveness of reducing diets, and we have found that true in general. Low caloric diets used in the hospital seemed to be less effective in these persons than in other obese persons. Yet their basal metabolic rates were not abnormally low. The obesity was confined to the trunk, face and proximal parts of their extremities. Pale striae were present in 3 and brownish striae in 1. Hirsutism of some degree was found in 3, in 1 (case 18) requiring biweekly shaving of the face. Menstruation was irregular in 3. Four complained of a tendency to ecchymoses, minor trauma producing discolored bruises. In 2 cases a mottled dusky cyanosis of the extremities was noted.

Neither acne nor polycythemia was present. Oral glucose tolerance tests showed a diabetic type of curve in 3; in 1 it was normal, and in 2 it was not measured. One patient (case 17) had received insulin previously for glycosuria and hyperglycemia. All complained of moderate to severe headaches, localized in the occipital region in 4, in the frontal in 1 and in the vertex in 1 (table 2).

Albuminuria was absent, although in at least 3 cases blood pressure was at relatively high levels and the disease had been present for a considerable period of time. Abnormal microscopic elements in the urine were few or absent. When the intake of fluids was compared with the urinary output, 3 of these patients appeared to show usually a relatively low urinary volume. This condition was not consistent throughout the period of observation, but it was noted that for many days the output of urine would vary from about 600 to 800 cc. per day, while the intake was 2,000 cc. or more. In 1 (case 22), who was carefully studied by control of the intake of fluids, the urine output remained below 800 cc. a day for thirty-four days, often being below 500 cc., and did not rise when the fluid intake was increased from 800 to 2,000 cc. per day. There was no gain in weight despite this discrepancy; the patient manifested profuse sweating. Antidiuretic substance was found in her urine.

In 3 cases, plasma sodium determinations were made and were within normal limits. Plasma chloride levels, however, appeared to be slightly higher than are usually found in this laboratory, varying from 105 to 110 milliequivalents per liter. In the 3 cases in which it was measured, the ratio of sodium to chloride was lower than that found by Selye[5] in many hypertensive patients. In 3 patients in the group not responding to a low salt regimen, this ratio was elevated above 1.44, Selye's upper limit of normal.

Five milligrams of desoxycorticosterone acetate was injected intravenously or 10 mg. intramuscularly in 4 of these patients. These single injections were followed in all cases by prolonged elevations of the blood pressures, lasting from one to three days. Such a response is unusual, as most hypertensive persons will not derive such a long-sustained elevation of blood pressure from a single dose of this substance.

The general body configuration of these patients is worthy of comment. It resembles in some respects that seen in Cushing's syndrome. When other suggestive signs and symptoms of Cushing's syndrome were looked for, some of them were found; but in no case were all of the classic observations of this condition present.

TABLE 2.— *Signs Common to Subjects Responding to Dietary Restriction of Sodium Chloride*

Case No., Patient, Sex	Body Weight, Pounds	Striae *	Hirsutism †	Irregular Menses	Tendency to Ecchymoses	Dusky Cyanosis and Mottling	Headaches: Location	Headaches: Degree	Glucose Tolerance Curve ‡	Albuminuria	Response of Blood Pressure to Desoxycorticosterone Acetate	Low Urine Output §	Plasma Electrolytes (Fasting): Sodium, mEq./L.	Plasma Electrolytes (Fasting): Chloride, mEq./L.	Plasma Electrolytes (Fasting): Carbon Dioxide, mEq./L.	Plasma Electrolytes (Fasting): Ratio Sodium/Chloride	Comment
14 A. F. ♂	126	0	0	..	0	0	.....	None	.....	0	..	0	143.8	94	29.4	1.53	Mild hypertension and renal calculus
15 W. D. ♂	171	0	0	..	0	0	Occipital	Moderate	.....	+	..	0	143.0	105	26.9	1.36	Moderate neurogenic hypertension
16 C. O. ♀	122	0	+	+	0	0	Occipito-parietal	Severe	Normal	0	..	0	.....	100	28.3	....	Mild neurogenic hypertension
17 L. S. ♀	191‖	+	+	+	+	0	Occipital	Moderate	Diabetic	0	+¶	0	.....	105	....	....	Pseudo-Cushing's syndrome #
18 L. C. ♀	259‖	+	+	+	..	..	Frontal	Moderate	Normal	0	+¶	+	141.6	109	27.1	1.30	Pseudo-Cushing's syndrome #
19 I. H. ♀	171‖	0	0	0	+	+	Occipital	Severe	.....	0	+¶	0	145.3	110	20.8	1.32	Pseudo-Cushing's syndrome #
20 M. P ♀	154‖	0	0	0	..	..	Vertical	Severe	.....	0	..	..	.....	106	....	....	† Pseudo-Cushing's syndrome #
21 M. L. ♀	205‖	+	0	0	+	0	Occipital	Severe	Diabetic	0	+¶	+	140.7	110	23.7	1.28	Pseudo-Cushing's syndrome #
22 F. R. ♀	253‖	+	+	+	+	+	Occipital	Moderate	Diabetic	0	..	+	.....	...	....	....	Pseudo-Cushing's syndrome #

* Pale, except those in case 21, which were brownish; they were distributed on arms, thighs and abdomen.
† Hirsutism—on face, chest or abdomen.
‡ By oral method.
§ Low urine output means that there was considerable discrepancy between the intake and output of fluids for periods of many days at a time, the urine volume being one quarter to one half of the intake. There was no correlation between this finding and the season of the year.
‖ Obesity of trunk, face and proximal parts of extremities ("buffalo" type).
¶ The patient's blood pressure became significantly elevated above control values, after one injection of 5 mg. desoxycorticosterone acetate intravenously or intramuscularly and remained elevated for one to three days.
# See text.

COMMENT

From a review of our cases, it would appear that restriction of sodium chloride in the diet, either by the use of the "rice diet" of Kempner or by other means, is usually ineffective when the condition is advanced and therapy becomes mandatory. In one type of case, however, restriction of sodium chloride appears to be definitely beneficial with respect to the level of blood pressure. In this type, restriction of salt appears to lower blood pressure when other factors are controlled,

5. Selye, F. L.: Biochemical Changes in Hypertension, Canad. M. A. J. **57**: 325-330, 1947.

and addition of salt to the diet appears to raise it. The clinical observations in this group of patients are suggestive of an alteration in some of the functions of the adrenal cortex, although laboratory confirmation of such disturbances is so far lacking. Such a disturbance, if present, is not advanced enough to produce the classic observations of Cushing's syndrome, although many of its manifestations seem to be present to some degree. The condition in these cases has been called "pseudo-Cushing's syndrome."[6]

In view of the apparent differences in this obese group of patients from the usual patients with arterial hypertension, it is possible that these patients suffer from a different condition of which hypertension is only one manifestation. Once aware of this condition, one finds it relatively easy to identify. Recognition makes dietary restriction of salt of more certain benefit to the patient and avoids for the patient the inconveniences of trial and error methods of dietary management.

The other patients who responded to the restriction of salt (cases 14, 15 and 16) either exhibited considerable susceptibility to psychotherapeutic influences, being easily suggestible, or were in mild stages of the disease. The response of their blood pressures to salt restriction occurred after a later interval than it did in the "pseudo-Cushing" group. In 1 (case 14), the addition of salt to the diet had no effect; in another, changes which had occurred were somewhat reversed. Other influences than dietary ones cannot, therefore, be excluded in these 3 cases.

In general, every effort was made in this study to exclude the effects of influences other than dietary ones. One of these, hospitalization, has proved a very significant one in some patients (table 3).[2] It has therefore been our practice to require a control period in the hospital of about a month's duration before instituting any therapeutic procedure. In only 3 patients (cases 13, 20 and 22) was no control period used, although observations on them in the outpatient department had indicated sustained high levels of blood pressure for long periods. In 3 cases the control period was two weeks, and in the remainder (9 in the first group and 7 in the second, table 1) it lasted three to six weeks or more. If this relatively long period had not been used, the diets would have appeared beneficial in 5 of the group in which a poor response was noted, and more beneficial in 3 of the others. It seems possible, therefore, that some reports of good results accruing from low salt diets have not taken these other influences into account.

TABLE 3.—*Effect of Hospitalization on Blood Pressure* *

Case No.	Patient	Sex	Average Blood Pressure First 7 Days After Admission, Mm. Hg.	Control Period, Days	Average Blood Pressure Last 7 Days of Control Period, Mm. Hg.	Change Control Period, Mm. Hg.	Total Change Control and Diet Periods, Mm. Hg.†	Additional Influences in Control Period: Bed Rest	Additional Influences in Control Period: Amount of Salt, Gm.
			Poor Response to Salt Restriction						
3	S. K.	♀	243/126	13	232/119	−11/− 7	−19/− 7	+	−
4	V. R.	♀	193/126	39	168/113	−25/−13	−24/−16	0	−
5	F. W.	♀	200/130	40	183/115	−17/−15	−36/−12	0	−
6	K. E.	♀	169/110	39	187/126	+18/+16	.....	+	−
7	D. R.	♀	218/151	11	217/150	− 1/− 1	.....	+	−
8	P. R.	♂	175/100	12	166/ 92	− 9/− 8	.....	+	2.0
9	A. K.	♂	212/122	26	204/119	− 8/− 3	−15/− 9	0	−
10	L. N.	♂	189/127	51	198/134	+ 9/+ 7	.....	0	−
11	A. P.	♂	259/169	31	251/163	− 8/− 6	−33/− 7	+	1.0
12	A. B.	♂	222/160	28	222/159	0/− 1	.....	0	−
13	T. A.	♂	205/140	13	201/150	− 4/+10	.....	+	2.0
			Significant Response to Salt Restriction						
14	A. F.	♂	165/103	32	168/112	+ 3/+ 9	.....	0	−
15	W. D.	♂	195/129	28	195/132	0/+ 3	.....	0	−
16	C. O.	♀	167/111	34	156/107	−10/− 4	−40/−18	+	−
17	L. S.	♀	200/115	21	191/108	− 9/− 7	−31/−27	0	−
18	L. C.	♀	180/112	23	199/123	+19/+11	.....	0	−
19	I. H.	♀	166/121	35	161/110	− 5/−11	−29/−29	0	−
20	M. P.	♀	220/131	15	140/ 95	−60/−36	.....	+	1.0
21	M. L.	♀	183/113	105	176/119	− 7/+ 6	.....	0	−
22	F. R.	♀	185/ 97	50	127/ 77	−58/−20	.....	+	1.0
23	D. B.	♀‡	172/111	85	143/100	−29/−11	.....	0	−
24	J. O.	♀‡	175/110	20	120/ 80	−55/−30	.....	0	−
25	E. C.	♀‡	200/116	39	179/110	−21/− 6	.....	0	−
26	L. S.	♀‡	170/110	26	164/105	− 6/− 5	.....	0	−

* Average figures for first seven days of control period not available in cases 1 and 2. Each was controlled for eight weeks.
† See table 1. This column reflects the changes which might have been attributed to salt restriction if control periods had not been used. Only the patients whose blood pressures fell during control period are listed.
‡ Studied for effect of hospitalization only.

SUMMARY AND CONCLUSIONS

Twenty-two patients with hypertension were placed on diets low in sodium chloride in the hospital in an attempt to evaluate the effects of such diets on the levels of their blood pressure. The effects of hospitalization and psychotherapeutic influences were controlled so far as possible.

In 13 patients, most of whom exhibited the disease in its severer stages, the response to salt restriction was poor. Three additional patients with milder forms of the disease manifested a lower level of diastolic pres-

6. By Dr. Willard M. Allen, of Washington University School of Medicine. It is probable that these cases are similar in many respects to those reported by Herrick, W. W.: Hypertension and Hyperglycemia, J. A. M. A. **81**: 1942 (Dec. 8) 1923. In a review of 218 cases of "essential hypertension," Schroeder and Steele noted 7 cases which fitted into this category and 7 other obese women whose hypertension began with the menopause. In addition, 2 obese women exhibited elevated basal metabolic rates without hyperthyroidism. Some of these were benefited by restriction of dietary salt. Schroeder, H. A., and Steele, J. M.: Studies on "Essential" Hypertension: I. Classification, Arch. Int. Med. **64**: 927-951 (Nov.) 1939.

sure; in 1 of these the change which occurred was not reversed by the addition of salt to the diet.

A group of 6 female patients are described who exhibited obesity of a characteristic distribution, and some but not all of the signs of Cushing's syndrome. In these, levels of blood pressure appeared to be directly related to the intake of sodium chloride, being lower when salt was restricted and higher when it was added. These patients probably suffer from a disturbance of which arterial hypertension is only one manifestation. It is suggested that there is an alteration of some of the functions of the adrenal cortex in such persons. In general, when the disease was relatively advanced and treatment was mandatory neither restriction of salt nor the rice diet appeared to be of much benefit.

ABSTRACT OF DISCUSSION

DR. DAVID AYMAN, Boston: Dr. Schroeder has presented one of the first series of controlled—although limited in number—observations on the effects of the rice and salt-free diets. It appeared clear that Kempner's studies, as he reported them, did not include the controls necessary in any careful evaluation of blood pressure. The universal demand for the diet by patients followed the unfortunate newspaper publicity which greets the announcement of any new method or treatment, so that patients have placed themselves on the diet without medical care or forced physicians to put them on the diet. Kempner's methods in general consisted of brief periods of control before the diet, so that a large number of his patients have been placed on the diet either at once or within a few weeks after arrival at Duke University. Dr. Schroeder has attempted to avoid this source of error by waiting three or four weeks before starting the diets. However, even such a period of waiting before treatment is not adequately long. Dr. Schroeder recognized this when he demonstrated in several patients that hospitalization alone caused significant drops in blood pressure, in 1 case to normal levels. It follows, therefore, that if all patients had been given the diet after thirty days of hospital rest and observation, further drop in blood pressure might well have occurred in some additional patients if he had waited ninety days before introducing the diet. Dr. Schroeder modified Dr. Kempner's study a bit by using a nightly barbiturate. This, together with a quiet hospital environment, might be enough gradually to lower blood pressure by progressive relaxation. The study that Dr. Schroeder has today presented is clearly of a small number of patients. I think, therefore, that on the basis of such a small number of patients it is unwise to estimate even roughly that blood pressures in 10 per cent of hypertensive patients will drop to normal levels on a salt-free diet. The effect of rapid weight reduction on blood pressure, as well as any specific diet effect, is involved in the studies of Kempner and Schroeder. Kempner admitted that it is common to have decided weight loss in the first twenty days of the diet. Schroeder's cases show the same weight drop. I would like to ask Dr. Schroeder whether he noticed any decreases in heart size, favorable changes in electrocardiograms or improved changes in the fundi, all of which Dr. Kempner frequently found with the rice diet. The diminution in heart size and improvement in electrocardiograms, nonprotein nitrogen levels and cardiac state, as reported by Kempner, merit some mention and some explanation. In Dr. Kempner's papers the striking effects on blood pressure, heart size, electrocardiographic observations and fundi, have been most often in patients with congestive heart failure or nephritis. In these two conditions the rice diet, with its restrictions of sodium and protein, is merely a more stringent form of low sodium and low protein diets already used for heart failure and nephritis.

DR. MILTON LANDOWNE, Chicago: When a patient is put in a hospital it may take a while for his pressure to become "stabilized," and during that period his blood pressure may fall. The reduction of blood pressure to a more basal level by hospitalization alone might also have been accomplished by some other form of therapy for the ambulatory patient. Once the pressure has been lowered by hospitalization, however, the other therapy may not reduce it further. That may have been partly in the mind of Bryant and Blecha when they reported that a majority of ambulatory patients on a very low salt diet had a reduction of blood pressure. Because of their report my co-workers and I undertook to study a small group of patients in the clinic rather carefully, and we attempted to control the therapeutic and psychotherapeutic effects of placing them on a rigidly restricted salt diet. We put these patients on a diet calculated to be adequate except for its sodium content of less than 300 mg. per day. In addition, we gave these patients medication consisting either of lactose or of 4 Gm. of sodium chloride a day given in identical manner. We did twenty-four hour urinary analyses for sodium and creatinine once a week as a check on how well the patients were following the diet. I do not propose to report here on the results of our study, but will mention two pertinent points: First, only 1 out of 3 patients whom we had expected to be on the diet stayed within the limits of the diet as we defined it. Therefore, without urinary checks, one cannot assume that the patient is following a salt-restricted program. There is no report from the Michigan group as to how many of their patients followed the diet. Our data indicate that 1 out of 3 patients whom we put on a diet restricted in sodium to considerably less than 0.5 Gm. of sodium per day actually followed that diet to that degree. Second, while we did find an occasional patient whose blood pressure fell during the period of effective sodium restriction, there was certainly no overwhelming difference between the control and the experimental subjects when the variable factor was entirely or largely limited to the salt received.

DR. FREDERICK M. ALLEN, New York: Experiments which seek to extenuate the former error of denying the pressor effect of salt by depicting it as small invite comments epitomized as follows: 1. Animal experiments conclusively prove pressure elevation by salt. 2. Allen-Sherrill (1922) excluded psychic, weight, protein and other factors in 280 cases during four years. 3. Even in this first use of diets capable of producing salt deficiency, supervision prevented dangers. 4. Brief observations on a few patients of the class recognized as refractory by myself, Kempner and Grollman establish no scientific conclusions for the whole subject. 5. Just as in diabetes, failures in worst cases do not invalidate diet principle. 6. My distinction, twenty-two years ago, between symptom and disease of hypertension explains benefits not measured merely by pressure reduction and often apparent after years in initially refractory cases. 7. Symptomatic variations, physical and psychic influences must be weighed against death rate unaltered by symptomatic palliations, and rarity of hypertension among the insane with utmost excitations and depressions. 8. Preliminary rest makes pressure reduction in subsequent brief diet experiments appear as small as possible but misses distinction between transitory symptomatic effect and permanent specific diet effect. Diet keeps all but extremely hypertensive patients active and improved. 9. Frequent clearing of retinitis, congestive failure, headaches, dyspnea and other symptoms is unmistakable. 10. Permanent effects are paramount. Though I oppose operation, necessity of evaluating results in chronic disease during many years is recognized by surgeons, not by our medical opponents. Kempner's duplications of my results should prove similarly durable unless superfluous restrictions discourage the necessary lifelong fidelity. 11. I first demonstrated that vascular atony of shock requires sodium chloride solution, not plasma proteins. 12. Selye connects sodium chloride with etiology of hypertension. Therefore, though my research was cut off, I still submit that observations supporting salt restriction are superior in number, duration and validity. Appetizing diet encourages fidelity. Long ago, the public should have been taught to accept diet for hypertension as routinely as for diabetes. The waste of life during the past twenty years may continue for another ten years before all agree. My conclusion, based on unique experience in several thousand cases during twenty-eight years, is that saltless diet, especially when begun reasonably early, can specifically arrest

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progressiveness, prevent complications and thus provide the first real control of deaths from hypertension.

DR. EUGENE FOLDES, New York: In regard to the effects of various diets on arterial hypertension, I should like to call attention to the antiretentional dietary which I introduced fifteen years ago. This diet is based on the postulate that the water content of the blood, and thus the circulatory blood volume, vary with the water content of the rest of the organism, so that measures which reduce the water content of the body reduce the circulatory blood volume. The antiretentional diet is further based on the concept that reduction of the circulatory blood volume is followed by reduction of the blood pressure and aims at such reduction of blood volume and blood pressure by the administration of a regimen in which food substances are selected according to their effects on the water and mineral metabolism. Food substances having diuretic action, such as proteins and vitamins, are employed in liberal amounts, while food substances which may lead to liquid retention, such as carbohydrates, fats, sodium chloride and water, are used sparingly. I found this diet effective in many cases of arterial hypertension, and the results were confirmed by others. These therapeutic results, when compared with those obtained by the salt-free and the rice diets, are not unfavorable to the antiretentional dietary. The person suffering from arterial hypertension has functions and needs other than those determined by his blood pressure. These functions and requirements are not always well served by the salt-free and the rice diets. Both of these diets are unpalatable and monotonous. Further, for the human being, sodium chloride is not an indifferent chemical which can be introduced in excessively high or excessively low amounts without damage. The exhaustion and other serious consequences of considerable sodium chloride losses are well known and are further demonstrated in 1 of Dr. Schroeder's cases. Occurrences of pseudouremia and influences of sodium chloride deprivation on the carbohydrate metabolism, sexual function and the like should also be considered. As to the rice diet, it is not only salt free but it is also poor in proteins and rich in carbohydrates, a combination which may lead to fatty infiltration of the liver and to all the attendant disturbances. In addition, the rice diet is poor in some of the naturally occurring vitamins and these vitamins cannot be adequately replaced by the administration of a preparation. In contrast, in the antiretentional dietary, consideration is given to the patient's needs other than the regulation of the blood pressure.

QUESTION: Is it possible that salt restriction would be more effective if kept at 200 mg. as outlined by Bryant?

DR. HENRY A. SCHROEDER, St. Louis: The psychotherapeutic influences on the patients were controlled so far as possible, but I will agree with Dr. Ayman that putting a patient in a hospital for three months is a definite psychotherapeutic procedure. These patients were told when they were given rice or low salt diets that this was an experimental procedure, that there had been reports of its being of some benefit, but that we did not know whether or not it was beneficial, and we asked for their cooperation. I would like to stress that in no way have we reproduced the Kempner regimen, which I have no doubt is beneficial in a certain proportion of cases. We merely tried to find out whether the benefit lay in the diet itself or was due to other influences. We were unable to perform a clearcut experiment in any of our patients or to add certain things, like protein, amino acids or sodium, to the diet as we had planned, in order to answer this question. All of our patients lost some weight when on a diet either of salt restriction or of rice. There were changes in the heart size in some, but I believe that changes in heart size or in the electrocardiogram, particularly with respect to the inverted T wave, are functions of the level of blood pressure, and when the blood pressure came down we did notice such changes. Anything which will bring the blood pressure down will often produce these changes; there is nothing specific about the diet. Pyrogens will do it as well. Sympathectomy will do it. Any so-called specific or nonspecific procedure will do it. I think that Dr. Allen deserves great credit for having introduced the low salt diet into this country in 1922. My own personal interest in salt restriction goes back many years, particularly in regard to its effect on cardiac decompensation. Nothing would please me more than to find that salt restriction was of therapeutic benefit in all cases of hypertension. However, these are our results, and we must interpret them as carefully as we can. We cannot come to the conclusion that there is any specific benefit from salt restriction or from rice in all patients. I think it possible that in patients who do respond to a restriction of salt—and there are some whose response is dramatic—there is different causation, perhaps with more of an endocrine element than a renal or a nervous one. Those with the primary nervous or renal elements do not respond to these regimens as well as do the others. In reply to the question as to whether salt restriction would be more effective if kept to 200 mg. of sodium as outlined by Bryant, which is approximately 0.5 Gm. of salt, that is about the amount of sodium—200 mg.—or which is in the rice diet. We have used the 0.5 Gm. diet frequently.

DIAGNOSIS OF CANCER OF THE LARGE BOWEL

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The diagnostic criteria for advanced malignant disease of the large bowel are well recognized, but the diagnosis of early cancer and the differential diagnosis of benign polyps, diverticulitis and carcinoma require the closest cooperation of the clinician, the radiologist and the pathologist.

In a previous presentation of this subject, comprising a review [1] of 100 cases of cancer of the rectum, 100 cases of cancer of the left colon and 100 cases of cancer of the right colon, it was noted that the chief complaints of the patients could be placed in three groups (table 1):

TABLE 1.—*Symptoms of Carcinoma of the Colon and Rectum (300 Cases)* *

Symptom	Location of Carcinoma, Percentage of Patients: Rectum	Left Colon	Right Colon	Total, Percentage
Blood in stool	86	46	9	46
Altered bowel function	79	82	81	80
Abdominal cramps or pain	7	77	87	57
None	2	2	3	2.3

* Over 80 per cent of all patients with carcinoma of the colon and rectum complained of rectal bleeding.

SYMPTOMS

1. Rectal bleeding. Over 80 per cent of all patients with malignant disease of the large bowel will have associated rectal bleeding. This is the most significant symptom of cancer of the colon and rectum.

2. An alteration or change in bowel function. The mildly constipated patient who has been taking an

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From the Department of Surgery (Dr. Swinton) and the Department of Radiology (Dr. Hare), The Lahey Clinic, and the Department of Pathology, New England Deaconess Hospital (Dr. Meissner), Boston.

1. Swinton, N. W., and Higgenbotham, J.: The Diagnosis of Carcinoma of the Colon and Rectum, S. Clin. North America **18**:733-743 (June) 1938.

occasional laxative for years presents little of significance, but if increasing constipation or some other change in bowel function has been noted within recent months, complete studies are indicated.

3. Abdominal pain. This is usually a crampy, colicky-like pain associated with varying degrees of obstruction or nodular extension of the disease.

Fig. 1.—Benign mucosal polyp, showing regularity of gland, maturity of cells and absence of stromal invasion (eosin methylene blue stain × 50).

Ninety-eight per cent of the patients at the clinic with proved carcinoma of the colon or rectum complained of one or more of these three symptoms. There are other signs and symptoms which may be significant. Unexplained anemia is frequently associated with a neoplasm of the right colon. An abdominal tumor may have its origin in the colon without associated colon or rectal symptoms.

Rectal bleeding, the commonest complaint of patients with malignant disease of the colon and rectum, in our experience has been the least well evaluated by physicians. It has too often been casually accepted, probably because it is so commonly experienced. Nearly all of us at one time or another have noted a drop or more of blood on the toilet tissue or in the bowl. Patients, however, are becoming increasingly cancer conscious. The publicity being given the subject of cancer, its early diagnosis and the significance of bleeding from any of the body orifices has resulted in an increase in the number of patients consulting their physician at the first appearance of rectal bleeding. It is of the utmost importance, therefore, to all of us, as physicians, that an adequate examination be made of these patients when they first present themselves.

Any patient with rectal bleeding should be considered to have malignant disease until proved otherwise. Any patient with rectal bleeding, a change in bowel function or unexplained abdominal pain should first have a careful inspection of the perianal area and anal orifice. Anal carcinoma is rare but does occur. A careful digital examination of the anal canal and rectum should follow. Fifty per cent of cancer of the large bowel can be palpated in this manner.

SIGMOIDOSCOPIC EXAMINATION

After digital examination of the rectum, an anoscopic visualization of the anal canal and a sigmoidoscopic examination of the rectum, rectosigmoid and low sigmoid regions should be performed. The origin of rectal bleeding most frequently is in the anal canal. Hemorrhoids, fissures, inflammatory conditions and other common diseases found in this region should be accurately classified. Hemorrhoids and hypertrophied anal papillae or true polyps of the anal canal rarely, if ever, result in malignant degeneration.

The majority of tumors will be found above the anal canal. They may be benign mucosal polyps or malignant tumors (fig. 1). The frequency and significance of benign mucosal polyps of the colon and rectum are not generally appreciated. Swinton and Haug [2] and Helwig [3] reported large autopsy series, giving an incidence of mucosal polyps of the terminal bowel of 7 to 10 per cent for patients dying from all causes. There is an increasing incidence with age and a high percentage of multiplicity of these tumors. The relationship between these polyps and cancer is definitely established. All stages in the development of adenocarcinoma can be demonstrated histologically between polyps of this type and advanced malignant disease (figs. 2 and 3). Mucosal polyps of the large bowel are true tumors and definite premalignant lesions.

The criteria as to when a digital and sigmoidoscopic examination of the terminal bowel should be done are not adequate for the detection of premalignant lesions. Only one third of patients with benign mucosal polyps of the rectum and colon complain of rectal bleeding. A very small number have associated obstructive symptoms.

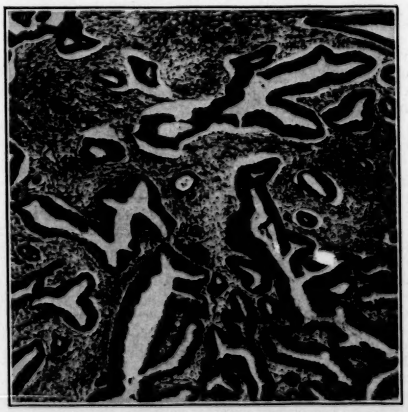

Fig. 2.—Early carcinoma arising at the base of a polyp, with atypical glands, atypical cells and invasion of stroma (eosin methylene blue stain × 50).

It is our firm conviction that, if large numbers of these premalignant lesions are to be discovered, not only must every patient with any symptom referable to the

2. Swinton, N. W., and Haug, A. D.: The Frequency of Precancerous Lesions in the Rectum and Colon, Lahey Clin. Bull. 5: 84-88 (Jan.) 1947.

3. Helwig, L. C.: The Evolution of Adenomas of the Large Intestine and Their Relation to Carcinoma, Surg., Gynec. & Obst. 84: 36-50 (Jan.) 1947.

large bowel be carefully investigated but sigmoidoscopic examinations must be a routine part of every complete general examination. Only when a sigmoidoscope is considered as important a part of one's diagnostic equipment as the stethoscope, vaginal speculum, laryngoscope and otoscope will large numbers of these tumors be found and an appreciable number of patients saved from development of cancer.

Fig. 3.—Adenocarcinoma, moderate malignancy, arising in mucosal polyp (eosin methylene blue stain × 50).

DIFFERENTIAL DIAGNOSIS—BENIGN AND MALIGNANT POLYPS

The differential diagnosis between benign and malignant polyps is, at times, extremely difficult. When these tumors are within reach of the examining finger the induration, fixation and firmness of malignancy is pathognomonic. The soft nonindurated mucosal polyps will rarely reveal any evidence of cancer. Usually, however, reliance must be placed on the pathologist for the differential diagnosis. Tissue should be removed from these tumors for histologic examination whenever they can be visualized. This can be done as an office procedure. One must realize, however, in doing this that there will occasionally be troublesome hemorrhage from such rectal biopsies. For accuracy in the differential diagnosis of malignant degeneration in these tumors it must be remembered that cancer can arise in any portion of a mucosal polyp. The entire polyp, together with its base, should be studied histologically before a final diagnosis of the nature of these tumors can be established.

Of late, increasing numbers of patients are being referred to us with a tumor of the rectum or sigmoid for whom a biopsy has been performed and a diagnosis of cancer established. A review of the microscopic slides of these specimens coming with the patients and repeated biopsies of these tumors have, many times, failed to confirm the diagnosis of cancer. We believe that there may be a tendency among pathologists not dealing with polyps in considerable numbers to diagnose some of these borderline lesions as malignant a little more often than seems justified.

The importance of the accuracy of the histologic diagnosis of these tumors (polyps) cannot be overemphasized. To a large extent, the decision as to the type and extensiveness of radical surgical treatment which will follow is based on the interpretation of the microscopic observations by the pathologist. The diagnosis of tumors in many other parts of the body as malignant growths may be of relative unimportance by comparison, since the treatment of a precancerous lesion and of cancer may often be similar or identical. However, when dealing with epithelial tumors of the large bowel, overenthusiasm in the diagnosis of malignancy may be extremely serious, since, with rare exceptions, the diagnosis of cancer is the only diagnosis which necessitates a radical surgical removal, frequently with permanent colostomy.

The microscopic recognition of cancer in a biopsy specimen removed from the rectum is not difficult if the tumor is well developed. The tumor shows atypical cells, irregularity of glandular structure and invasion of adjacent structures. There are borderline lesions, however, in which the criteria may not be so definite. The differential diagnosis between the benign but actively growing polyp and carcinoma arising in a polyp frequently must be made. The criteria used in this clinic for the differentiation have previously been outlined by Swinton and Warren.[4] The diagnosis is based primarily on anaplasia, irregularity of architecture and invasion, at least two of the factors being present for the diagnosis of malignancy. One exception is definite lymphatic or blood vessel invasion, which is usually sufficient in itself for the diagnosis.

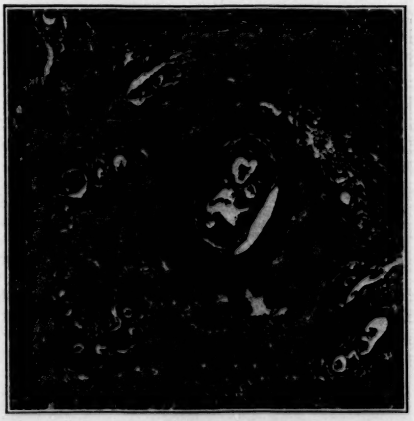

Fig. 4.—Adenocarcinoma with blood vessel invasion, showing invasion of large vein near center of field and attachment of tumor to vein wall (Verhoeff stain × 50).

Additional criteria which should be emphasized in the diagnosis of malignant disease in this region are mentioned.

1. Cancer must not be diagnosed on the mere presence of numerous mitoses in the tumor. Benign polyps often show many mitoses.

4. Swinton, N. W., and Warren, S.: Polyps of the Colon and Rectum and Their Relation to Malignancy, J. A. M. A. **113**: 1927-1933 (Nov. 25) 1939.

2. The presence of epithelial cells within vessels often occurs as an artefact produced by cutting the tissue. For the diagnosis of cancer, the intravascular epithelial cells should at least be associated with a thrombus and preferably by actually invading the vessel wall (fig. 4).

3. All portions of the biopsy must be examined before a negative report is made. Otherwise, a small focus of malignant change may be overlooked.

4. The diagnosis of cancer should never be made on borderline evidence. The pathologist should not feel compelled to diagnose tissue which is inadequate. The clinician and pathologist must both appreciate that repeated biopsies may be necessary before a definite decision can be made.

ROENTGENOGRAPHIC EXAMINATION

When symptoms suggest the possibility of organic disease in the colon or when examinations, as already discussed, have not revealed the origin of rectal bleeding or other abnormalities of bowel function, further examinations must be made of that portion of the colon above the reach of the 10 inch (25 cm.) instrument. For this region reliance must be placed on the observations of the radiologist. Malignant disease found in this region will approximate 30 per cent of the cancer encountered in the colon and rectum.

Patients selected for radiologic study of the colon should be selected on an individual basis and only after a careful history has been taken and physical, digital and sigmoidoscopic examinations of the lower bowel have been performed. It must be remembered that radiologic studies are not only important from the point of view of making an original diagnosis but also may be indicated to determine the presence of multiple lesions. In our experience, 42 per cent of the polyps found have been multiple. Thus, the multiplicity of both benign and malignant tumors should be considered.

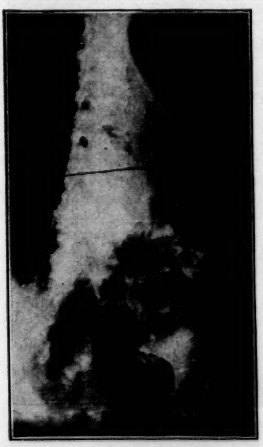

Fig. 5.—History of increasing constipation with loss of weight and rectal bleeding. On proctoscopic examination a mass was demonstrated in the lower left quadrant of the abdomen. Results of sigmoidoscopic examination were negative. A barium sulfate enema without preparation showed a tumor of the ovary with small bowel obstruction.

When advanced or large tumors of the colon are present, the preparation of the colon before radiologic studies are made is probably not too important, but if early or small lesions are to be demonstrated, the colon must be free of fecal material. It is our policy to prepare the colon for this purpose by giving 1½ (44 cc.) to 2 ounces (59 cc.) of castor oil the night before examination. A vigorous cathartic should not be given when an acute inflammatory process, ulcerative colitis, intestinal obstruction or appendicitis is suspected (fig. 5).

On the morning of the examination, a tap water or saline enema is given three hours before the barium sulfate enema. If sigmoidoscopic examinations are performed using this same preparation they should be made two to three hours before the barium sulfate enema radiograph is made, to allow evacuation of air which usually enters the colon at the time of the sigmoidoscopic visualization.

Fig. 6.—Colon polyp demonstrated by contrast air enema.

The routine barium sulfate enema radiograph is performed at the clinic as follows: a solution is made of 1 cup (235 milliliters) of barium sulfate plus 2 teaspoonfuls (8 to 10 milliliters) of tannic acid to each quart (0.95 L.) of warm water. The barium solution is allowed to enter the bowel slowly, the patient turning from side to side after filling of the ampulla so that clear visualization of the sigmoid can be obtained, particularly of those blind loops which extend posteriorly. After complete filling and observation fluoroscopically, roentgenograms should be taken in the posteroanterior and oblique positions so as to demonstrate all coils of the sigmoid. When a search is made for a lesion at the ampulla, lateral views of the ampulla should also be taken. The patient is then allowed to evacuate the colon and the three roentgenograms of the colon are again taken.

After this examination, if there is still a question of a lesion, particularly a polyp, a double contrast air enema of the colon should be considered.

There has been a tendency, probably more among clinicians than radiologists, to overemphasize the value of the contrast air enema. For those lesions involving the bowel the usual barium sulfate enema radiograph

is usually adequate. There are certain lesions which do not involve the bowel musculature, but which arise from the mucosa and extend into the lumen of the bowel, such as polyps, which can be better demonstrated by the contrast air technic (fig. 6).

When contrast air studies of the colon are made, a preparation similar to that already mentioned should be given. It is our policy at the clinic to carry out this study at a separate examination using a second preparation. A small amount of barium sulfate, a mixture of 1 cup to a quart of water, is used and the ampulla and sigmoid filled under fluoroscopic control. The patient is then allowed to evacuate and the colon filled with air. This allows an adequate demonstration of the mucosal markings of the colon. Stereoscopic roentgenograms are necessary for the most accurate study. These are taken with the patient in the prone and slightly oblique positions to demonstrate the coils of the sigmoid in relief. Both roentgenograms are taken while the patient holds a single breath to avoid motion. Even with examinations of this type we have had difficulty in demonstrating small mucosal polyps above the reach of the 10 inch (25 cm.) instrument. It has been our policy when such polyps are encountered to repeat the radiologic studies after a short interval, identifying the tumor at a second examination in the same location as that discovered at the first before submitting the patient to operation.

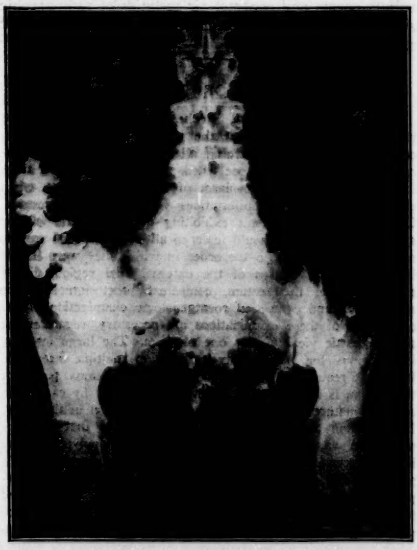

Fig. 7.—Demonstration of mucosal pattern in the large bowel. The loss of pattern in the rectum with irregularity is due to a large carcinoma of the rectum.

The limitations of the radiologic investigations of the rectum and sigmoid colon must be thoroughly appreciated. For the purposes of this presentation 161 cases were reviewed in which a barium sulfate enema roentgenogram of the colon was performed after a careful history, physical examination, digital examination of the anal canal and sigmoidoscopic examination of the rectum and lower sigmoid. The results of this study are shown in table 2.

This reveals that it is not possible at the present time with our present known radiologic technics to diagnose

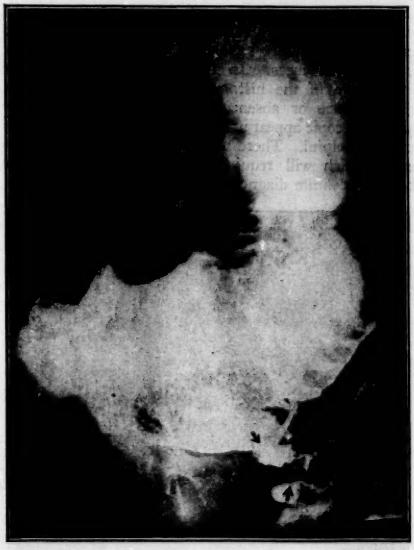

Fig. 8.—Diverticulitis with large bowel obstruction simulating a malignant growth.

many of the lesions of the ampulla of the rectum, the rectosigmoid area and, in certain instances, in the distal part of the sigmoid (fig. 7). The diagnosis of lesions of the colon beyond the reach of the sigmoidoscope is considered accurate. The bowel is usually accurately

TABLE 2.—*Results of Radiographic Studies of Colon and Rectum (Barium Sulfate Enema and Contrast Air Technics)*

	Number of Patients	Percentage
Studied	150	..
Rectal bleeding	62	41
Other symptoms	88	59
Polyps visualized with sigmoidoscope	15	..
Polyps visualized with radiograph	5	..

observed in roentgenograms both in the full and empty states, particularly in the empty in which the mucosal markings are well demonstrated. The use of tannic acid has improved our previous technics. It must be emphasized again, however, that even in this region of the bowel, radiologic studies are not perfect and no hesitation should be made in repeating such studies when the diagnosis is uncertain.

Retained barium in the colon may be a serious complication at the time of operation. When operation

is to be performed soon after the barium mixture has been introduced into the colon, cathartics and enemas may be necessary to remove such barium before the surgical procedure is undertaken.

Much has been said and written on the differential diagnosis of organic disease of the colon. In our experience, the most important problem has been the differential diagnosis between malignant disease and diverticulitis of the sigmoid. This is a problem which cannot be definitely settled by radiologic study alone in many instances. In this group of patients, the importance of the history and physical observations, the presence or absence of rectal bleeding and the sigmoidoscopic appearance of the bowel below the lesion may be helpful. There will be a group of cases, however, which will require actual surgical exploration before a definite diagnosis can be established.

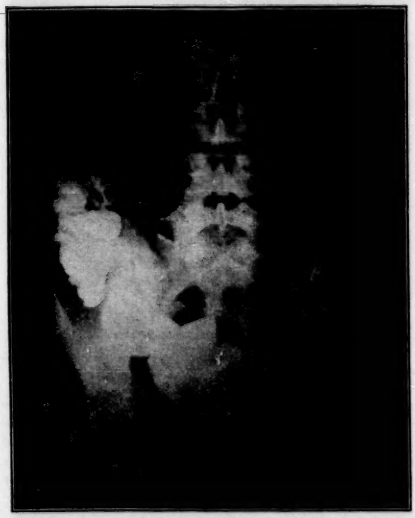

Fig 9.—Large polyp of the sigmoid colon simulating a malignant growth.

From the radiologic point of view the presence of a "shelf" at the beginning and at the end of the filling defect is strong evidence of malignant degeneration. The fact that mucosal markings of the colon in the involved lesion are usually destroyed when carcinoma is present, whereas they remain intact in diverticulitis, has not been of much assistance to us. The lesions of diverticulitis usually involve a larger portion of the colon than does carcinoma, but this is not pathognomonic (fig. 8).

SURGICAL EXPLORATION

There will also be a few instances in which the differential diagnosis between benign and malignant polyps cannot be established without surgical intervention.

On exploration, the differential diagnosis between cancer and diverticulitis of the sigmoid frequently cannot be established on inspection and palpation of the lesion. In these instances it has been our policy to carry out a local resection of the involved bowel and have an immediate histologic examination performed. The pathologic recognition of cancer of the colon when the entire specimen is thus submitted usually is not difficult. Further immediate surgical steps can then be planned accurately on the basis of this examination.

When a polyp is found in the lumen of the colon through a colotomy incision, in most instances a long pedicle of normal mucosa will be encountered. Local excision is adequate for tumors of this type even though ultimate histologic study may at times reveal areas of early malignant degeneration. Local resection of the bowel and tumor may be necessary before a final decision from the pathologist can be given as to the presence of malignant disease and the extent of resection indicated (fig. 9).

SUMMARY

The symptoms and methods of examination necessary for the diagnosis of cancer of the colon and rectum are reviewed. The necessity for the routine use of the sigmoidoscope in every physical examination of adult patients for the detection of premalignant lesions is emphasized. The criteria for the histologic diagnosis of malignant disease in this region are given. The tendency of many pathologists to "overdiagnose" borderline lesions of this type is mentioned. The indications for and the technic of radiographic studies of the colon are given. The limitations of the barium sulfate enema and contrast air technics of radiographic study of the colon and rectum in the diagnosis of cancer are discussed.

ABSTRACT OF DISCUSSION

Dr. Harry M. Weber, Rochester, Minn.: It is most important to remember that the patient with cancer of the colon may exhibit one, several, all or none of the symptoms of the disease that have been listed. Certainly there is a stage in the development of neoplasm of any internal organ when there are no clinical manifestations whatever of its presence. Obviously, then, a patient exhibiting one or several of the symptoms mentioned should undergo all of the special examinations described and in the order in which they were listed: inspection and palpation of the external anal region, digital examination of the rectum, competent proctosigmoidoscopic examination and competent roentgenologic examination of the colon. All of these examinations are necessary, regardless of the diagnostic yield of any one of them. The large intestine is notorious for its capacity to develop multiple neoplastic lesions. Frequently, for instance, an adenomatous polyp of the rectum is accompanied, followed or preceded by carcinoma of more mature proportions at a more orad level in the colon. Dr. Swinton and his co-workers pointed out that there is no certain way of knowing that any intestinal polypoid lesion is not cancer short of microscopic examination, not only of a part of the lesion but of the entire lesion. For practical purposes there is no reliable gross pathologic diagnosis of benignancy, once the presence of neoplasm is established. Hence such a polypoid lesion must be extirpated in toto, if for no other reason than to become certain of its malignant or benign nature by careful histologic study. To keep such a lesion under observation in situ until it shows advancing growth, induration, extension or other more definite evidence of malignant neoplastic change is to gamble unnecessarily with the patient's longevity. It is not certain that all cancers of the large intestine begin as polypoid lesions, but it is certain that a great many of them do. Thus the early diagnosis of intestinal cancer, even of intestinal precancer, is an actual possibility in this

day, and this diagnosis consists in the recognition of the small polypoid lesion. If such a polypoid lesion proves to be an adenomatous polyp it may be cancer at the time, but, if it is not, it will almost surely be cancer some day if its bearer lives long enough. This fact makes the clinical management of such a lesion obvious. With proctosigmoidoscopy and the roentgenologic examination of the colon, both assumed to be competently performed, we have the means of detecting these lesions even earlier in their development than they will manifest themselves by clinical signs and symptoms.

DR. WILLIAM H. DANIEL, Los Angeles: Dr. Swinton and his co-workers have clearly outlined the essential points in the diagnosis of cancer of the colon. Any of the three cardinal symptoms, however slight, are danger signals and must be proved innocent or serious by the proper examinations. The proctologist begins his search at the anus and attempts to visualize the bowel surface through the sigmoidoscope to at least 8 (20 cm.) or 10 (25 cm.) inches, using intravenous anesthesia if necessary. The barium sulfate enema should follow, to rule out higher lesions. If one is suspected, especially when streaks of dark blood are a constant observation, the double contrast enema should be given and repeated, to definitely rule out or confirm the presence of a polyp or beginning cancer. Since benign and malignant polyps are often associated with advanced carcinoma, it is reasonable to assume that the cancerous lesion itself may have originated as adenoma or a polyp. It is my practice and that of my colleagues to utilize the double contrast enema in every case in which a polyp is demonstrated by the sigmoidoscope, because of the tendency to multiplicity of polypoid lesions. In approximately 17,000 private patients there were 811 malignant lesions (4.7 per cent), including 32 anal epitheliomas and 74 polyps and adenomas (0.421 per cent). In the same group there were 581 patients (3.3 per cent) with benign adenomas and polyps. The majority of the polypoid lesions were found on routine sigmoidoscopic examination. Sections from several areas of the polyp should be studied by the pathologist in order to determine the degree of malignancy if present. I agree with the authors that the difference between a benign and malignant lesion depends on the pathologist who reads the slide. This is important, especially in the large villous adenomas, for which radical operation may be performed with sacrifice of the rectum when local treatment by fulguration usually is sufficient. The differential diagnosis between cancer and diverticulitis is not always simple. The roentgen observations may not be typical. A cancer may perforate the bowel, causing a perisigmoiditis and periproctitis. Surgical intervention is indicated when there is any doubt, and then it may be impossible to differentiate by palpation, especially when the cancer is surrounded by an inflammatory process.

DR. NEIL W. SWINTON, Boston: I did not intend to imply that we hold our radiologists responsible for the diagnosis of lesions in the lower 10 inches (25 cm.) of the bowel. I do not believe that we have a local situation entirely. A large number of our physicians who see patients with rectal bleeding, and do or do not carry out a digital examination, have a roentgenogram of the colon taken, using a barium sulfate enema, and then inform the patient that there is nothing seriously wrong. The patient must have a sigmoidoscopic examination, preferably before roentgenograms of the bowel are taken.

Medieval Football.—In his historical essay on Florentine football (*Calcio*), Count Giovanni Bardi, in 1688, described medieval football in detail. . . . To a certain extent, football in Italy succeeded and supplanted the tournaments. Thus a *Gala Calcio* was held generally on grand occasions such as the visit of a foreign potentate or an important marriage. Two of the most famous games were performed in February, 1530, despite the siege of Florence, and in the summer of 1558, on the occasion of the nuptials of Dona Leonora de'Medici . . . and Alphonse d'Este, son of the Duke of Ferrara.—Joseph, Ludwig H.: *Ciba Symposia*, March-April, 1949.

LABORATORY ASPECTS OF STREPTOMYCIN

EMIL BOGEN, M.D.
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In the few years since streptomycin was discovered and made available, it has already become established as an important agent in the treatment of many diseases.[1] Much enthusiasm has been evoked by the demonstration of its effectiveness in many hitherto refractory tuberculous lesions. Extensive resources have been utilized in its investigation, and much has been learned about it, but much still remains to be investigated.

Numerous other antibiotics besides penicillin and streptomycin have appeared promising from in vitro tests, but proved to be too toxic or feeble in animal experimentation. A few are undergoing trial, but none yet available have warranted clinical recommendation for tuberculosis. Many chemical agents have been found tuberculostatic, or tuberculocidal in vitro; some have shown promise in animal experiments, and several, including promin® (sodium p,-p'-diaminodiphenylsulfone-N,N'didextrose sulfonate), promizole® (4,2'-diamino-diphenyl-5'-thiazole sulfone) diasone® (disodium-formaldehyde-sulfoxylate-diamino-diphenyl-sulfone) and para-aminosalicylic acid, are being studied in patients, but none so far tested approach the effectiveness of streptomycin.

CHEMICAL STRUCTURE

The chemical structure of streptomycin as N-methyl-l-glucosamido-streptosido-streptidine has been confirmed. Several chemical variants, such as streptomycin B and dihydrostreptomycin, have been identified. Terminology may now be based chiefly on chemical identity, rather than on origin or properties, though synthesis still remains for the future. Newer preparations, such as the streptomycin calcium chloride complex and crystalline streptomycin, as well as the chloride and sulfate, are being produced in greater quantities, purer, more soluble and stable and less toxic than the crude materials available to the earlier workers. The lessened cost of streptomycin, with the lowering of the average daily dose and the shorter duration of the treatment, has greatly reduced the economic limitations to its use.

Colorimetric and fluorometric methods of chemical assay for streptomycin have been introduced, but simpler and more sensitive tests for the determination of streptomycin levels in blood or urine are wanted. The maltol test may have more general application in assays of concentrated preparations. Improved technics and greater experience with dilution, slide and plate methods of bioassay for streptomycin have increased confidence in their dependability. With the lower dosage now found effective, however, it appears unnecessary to perform the routine blood level studies earlier recommended.

ABSORPTION

The few reports of the rate of absorption of streptomycin from various channels in animals and human beings are based generally on earlier, less precise, bioassay technics. They show, in general, highest concen-

Read before the Section on Miscellaneous Topics at the Ninety-Seventh Annual Session of the American Medical Association, Chicago, June 24, 1948.

1. Waksman, S. A.: The Literature on Streptomycin 1944-1948, New Brunswick, N. J., Rutgers University Press, 1948.

trations immediately after intravenous, about one hour after intramuscular and still later after subcutaneous administration. The maximum blood level obtained after an injection approaches about twice the dose given divided by the body weight. Oral administration does not usually result in enough absorption to be shown by blood levels, though traces may be found in the urine. Absorption following inhalation into the lungs in the form of sprays or aerosols, or in micronized form, or following deposition in the upper respiratory passages, mouth or other sites has been reported with differing results. Few data are available regarding its absorption from the pleura or peritoneal cavities. Its absorption into the blood stream from intramuscular injection cannot be controllably delayed by suspension in beeswax and oil, as with penicillin; but there is inadequate information regarding this or the effects of local cold applications or epinephrine and the like on absorption rate or on possible differences in the absorption rates of various compounds of streptomycin.

Micro-Organisms Susceptible to Streptomycin

Actinomyces bovis	++
Aerobacter aerogenes	+++
Bacillus circulans	+++
Bacillus anthracis	+++
Bacillus subtilis	+++
Brucella abortus	+++
Brucella melitensis	+++
Brucella suis	+++
Clostridium butyricl	++
Clostridium septiel	±
Clostridium sordelli	±
Clostridium tetani	±
Clostridium welchii	±
Corynebacterium diphtheriae	+++
Eberthella typhi	+++
Erysipelothrix muriseptici	++
Escherichia coli	+++
Escherichia coli communior	++
Diplococcus pneumoniae	++
Haemophilus influenzae	+++
Haemophilus pertussis	+++
Klebsiella ozaenae	+++
Klebsiella pneumoniae	++
Klebsiella rhinoscleromatis	+++
Klebsiella granulomatis	++
Leptospira icterohemorrhagiae	++
Haemophilus ducreyi	+++
Mycobacterium tuberculosis	++++
Mycobacterium leprae	++
Mycobacterium smegmae	+++
Neisseria gonorrhoeae	++
Neisseria intracellularis	++
Pasteurella lepiseptica	++
Pasteurella pestis	+++
Pasteurella tularensis	++++
Proteus vulgaris	+++
Pseudomonas aeruginosa	++
Salmonella aertrycke	++
Salmonella enteritidis	+++
Salmonella paratyphi	++
Salmonella schottmulleri	++
Salmonella suipestifer	+
Salmonella typhi murium	++
Shigella paradysenteriae	+++
Staphylococcus albus	+
Staphylococcus aureus	++
Streptococcus fecalis	+
Streptococcus hemolyticus	++
Streptococcus viridans	+
Treponema pallidum	++
Vibrio cholerae	++

EXCRETION

Streptomycin is excreted, mainly in the urine, more slowly than is penicillin. It is eliminated chiefly by glomerular filtration. Carinamide or other substances which delay tubular excretion of penicillin do not, accordingly, have this effect on streptomycin. The effect of fluid restriction or other methods of lowering glomerular output appears slight. Streptomycin excreted in the urine may cause a weak reduction of ordinary sugar reagents, leading to reports of glycosuria. Other channels of excretion, such as the bile, feces and sputum, have been noted.

After the intramuscular injection of large amounts of streptomycin the concentration in the blood generally appears to be proportional to the amount given to any one animal. The rate of decline in this blood level does not appear to follow a straight line decrease, such as is seen with ethyl alcohol in the blood independent of concentration, but is closer to the logarithmic decline observed with penicillin or methyl alcohol, where the higher the blood level the greater is the amount excreted per time unit. After the injection of small amounts, streptomycin appears less regularly and disappears more rapidly from the blood stream. The rate of fall seems faster in dogs than in human beings. The concentration in the blood falls to one half of the previous level, in the average patient, in less than three hours, but may be greatly retarded in instances of renal retention.

DISTRIBUTION

Regarding the distribution of streptomycin throughout the bodies there are conflicting results based chiefly on studies in human beings and in a few cases on animal studies. It does not appear to diffuse through the tissue as readily as does penicillin, and there are differences in its final concentration in various organs. Thus, low levels have been noted in the spleen and liver and none in the brain. It appears to be distributed chiefly in the extracellular fluids, even that in the blood being found in the plasma rather than in the cells. More data are desired regarding the rate of distribution into various tissues and, also, the rate of return from these tissues back to the blood stream.

Trypan blue and certain other dyes show a selective predilection for the reticuloendothelial system and for lesions of tuberculosis. Streptomycin concentration in certain organs and lesions may be increased by coupling to the trypan dyes according to several studies. However, such increased concentration in the reticuloendothelial tissues or in the lesions do not appear to increase the therapeutic efficiency of the streptomycin.

TOXICITY

The toxicity of streptomycin has been found to be low for chick embryos, making possible the study of effects of streptomycin on mycobacteria, rickettsia and other organisms in such preparations, and the use of streptomycin to inhibit contaminations by susceptible organisms in the cultivation of resistant viruses, etc. Toxic effects have been noted with large doses in mice, rats, guinea pigs, rabbits, cats, dogs, monkeys and other animals. Most of our knowledge of the toxic properties of streptomycin, however, proceeds from the observations of treated patients.

Toxic manifestations may consist of allergic responses to pure streptomycin or to impurities in it. Sensitization may result from very small doses, by any route or even from casual contact by the nurse's handling of used syringes or in a neighboring patient exposed to escaping aerosol, with resulting dermatitis or other symptoms. Eosinophilia is frequent but unimportant. Acute histamine-like reactions early reported were probably due to impurities, but similar reactions may follow intravenous or even intramuscular injection in previously sensitized persons.

Local irritation seems chiefly due to impurities. It differs with various preparations of streptomycin and with different mode of administration. Simultaneous use of procaine hydrochloride is of little value in this connection. Renal irritation is common, but serious

renal damage leading to anuria appears to occur only with excessive dosage or with previous renal impairment leading to retention and high blood levels. Its danger is greatly reduced if not eliminated by the use of lower dosage. The hepatic and hemopoietic injuries encountered, though anticipated on the basis of animal experiments, have perhaps been coincidental, but must be seriously considered as they may otherwise be readily overlooked. Nutritional disturbances have been reported in animals as a result of elimination of vitamin forming intestinal bacteria by oral administration.

Complete and permanent loss of vestibular function develops in most patients receiving large doses for prolonged periods or who have excessive blood levels as a result of renal retention. With smaller, briefer or interrupted dosage the dysfunction may be only partial or temporary. With lower but still therapeutically active doses, vestibular damage may be completely averted. Experimentally similar disturbances have been observed in animals, especially the cat, and less readily in descending order in dogs, rabbits, rats and guinea pigs. Despite reports of degenerative changes in the vestibular nuclei, the exact nature and locus of the lesion involved is still obscure.

Deafness, though a distressing possibility, is so rare as to be practically negligible. The few cases reported have been generally among patients treated for tuberculosis meningitis, where the disease process, or the effects of the intrathecal injections, may be responsible. Local spinal cord or nerve injuries, including transverse myelitic syndromes, have resulted from intrathecal injection of large amounts or too concentrated or irritating preparations of streptomycin as well as from the trauma of frequent lumbar punctures. Paresthesias, especially of the face, are common, but fortunately mild and transitory. A few psychotic episodes have also been encountered. Other neurotoxic effects have been too rare or uncertain to establish etiologic relationship to the treatment.

Moderate but continuously sustained concentrations of streptomycin in the blood are more apt to be associated with toxic manifestations than are high peaks with intervening low levels. Toxicity may be reduced, therefore, by less frequent injections or by interrupted treatments. The clinical effectiveness of such dosage suggests that the therapeutic effect is not due to the same mechanism as that producing toxicity. Although antihistamine drugs may control some of the allergic manifestations of streptomycin sensitivity they do not seem to prevent vestibular damage. Desensitization by small doses has been reported as lessening vestibular damage, but this has not been confirmed.

MAXIMUM LIMITS

Deaths due to streptomycin have been observed in various species. The lethal component of commercial streptomycin has not been identified, and the mechanism of death in animals succumbing to it is still obscure. The earlier crude preparations of streptomycin killed animals in much smaller doses than do the purer products now available. There is also some variation in the toxicity of different lots of the same form. Nevertheless, much has been learned regarding lethal dose limits. Large animals withstand larger amounts than small ones. If the dose given is directly proportional to the body weight, however, large animals may be affected more than are small ones. If the effective dose depends on the total body fluids or of the blood volume rather than of the body weight, it would be more nearly proportional to the two-thirds or three-fourths power of the weight than to the weight itself. Blood levels after known doses of streptomycin on animals of different size tend generally to confirm these conclusions. Blood levels of 500 micrograms per milliliter or more are found in the blood taken after death in experimental animals.

Clinically vestibular toxicity has also been more pronounced in small patients when a uniform dose has been given to all, but it has been more pronounced in large men when the dose given is in proportion to the body weight. On the basis of animal experiments less than 20 Gm. of streptomycin sulfate or about 400 micrograms per kilogram of body weight injected intramuscularly at one dose may be expected to kill the average human being. Much less than this might be fatal to sensitive persons or with more toxic preparations. Actually as much as 3 Gm. of streptomycin has been given patients at a single time, and this amount in divided doses during each day has been taken by many patients for several months without a fatality.

THERAPEUTIC DOSAGE

Studies, both in experimental animals and in patients, have yielded extensive data regarding minimal, maximal and optimal therapeutic daily dosage and individual dose and frequency of administration. The administration of about 2.0 mg. per kilogram of body weight or 0.1 Gm. in an average man, giving peak blood levels of about 4 micrograms per milliliter, appears to be the lowest daily dosage which will affect tuberculosis. Better results are obtained up to about five times these figures, at 10 mg. per kilogram of body weight or about 0.5 Gm. per day in human beings, giving blood levels of about 20 micrograms per milliliter. Increasing the dosage above these figures gives little improvement in results.

The streptomycin therapeutic effect on the tubercle bacillus, at least, is exerted by high peaks with intervening low blood levels, as well as by moderately low but continuous blood level with persistent exposure of organisms to its action according to both animal and clinical observations. Recent reports suggest that the same may be true of penicillin, despite previous beliefs.

ANTAGONISTS

No specific antagonist to streptomycin, similar to the para-aminobenzoic acid-neutralizing sulfonamide drugs, or the penicillinase-inactivating penicillin, has been established. Lipositol, extracted from brain tissue and soy bean lipids, hydroxylamine, semicarbazide, cysteine, ascorbic acid, 2,3-dimercaptopropanol (BAL) and other reducing agents have been reported to interfere with streptomycin, but the mechanisms involved need further study. Salts, sugars, serum, peptones, tweens® (a series of polyoxyalkylene derivatives of hexitol anhydride partial long chain fatty acid esters) and other constitutents of the culture medium have also affected its activity in the hands of some workers, but not under other conditions. Increase in the activity of streptomycin as a result of the presence of enhancing factors has also been described.

BACTERIOSTATIC ACTION

Though all agree that streptomycin inhibits most tubercle bacilli in vitro, some observations suggest that streptomycin interferes with multiplication of tubercle

bacilli rather than with oxidation, growth or metabolic functions. Thus, tubercle bacilli inhibited by streptomycin have appeared larger and coarser or older than the same organisms growing in the absence of streptomycin. The tellurite test indicates that enzymatic processes continue in tubercle bacilli the multiplication of which has been inhibited by the presence of the antibiotic. Other studies of oxidative and other reactions have been made. Reports of bactericidal effects on stable cultures of tubercle bacilli or only on young growing cultures of these organisms, by several workers, have not been confirmed by others or in our laboratory (Western Trudeau Streptomycin Laboratory).

Delayed appearance of growth may be accounted for by complete inhibition of a fraction of the total organisms present rather than by partial inhibition of the entire culture. This is shown by a prolongation of the latent period before visible growth is noted, after which logarithmic growth curves manifest similar slopes. A variable latent period in the effectiveness of the antibiotic, that is, persistence of growth for a short period after the antibiotic has been added to a culture, especially with low concentrations of the antibiotic and large numbers of organisms, has been observed, though this seems to be absent when great excess of the antibiotic is present. On the other hand, despite clinical indications of prolonged effect, especially in animal experiments, in vitro observations fail to confirm the existence of a delayed persistent effect after the antibiotic has been completely removed from the culture medium.

STREPTOMYCIN RESISTANCE

The existence of streptomycin-resistant forms of acid-fast bacilli as of other organisms has been established. Repeated transplantation from subeffective concentrations of streptomycin in culture mediums has been used in order to obtain resistant forms, but, if heavy inoculations are made, gradual increase in concentration is unnecessary. Resistant tubercle bacilli have been rarely found in untreated patients. The general frequency of resistant forms in treated patients and their range and persistence has been confirmed. Discrepancies in the results with different methods of determining resistance have been reported. New mediums and culture methods are being developed which may facilitate the quantitative determination of resistant forms. Organisms resistant in vitro are also resistant to treatment in experimental animals and probably in patients.

Differences in the morphologic aspects, physiologic behavior, growth rate or virulence in the tubercle bacillus following the development of resistance have been reported, but my co-workers and I have not been able to confirm these observations at Olive View. Resistant forms may appear to differ morphologically from sensitive ones in the presence of streptomycin, since the resistant ones continued to multiply and so may show a greater variety of size and shapes, but when streptomycin is not present such difference may not be seen.

Stimulation of growth of susceptible organisms by concentrations too low to be bacteriostatic, or "hormesis," and the stimulation by, or even complete dependence of, resistant organisms on the antibiotic, such as has been reported for meningococci and other organisms, has also been reported with virulent tubercle bacillus, as well as with a related form. The progression of tuberculosis in patients after their organisms have become resistant has been interpreted by some workers as representing such "hormesis" in vivo.

Resistant forms sometimes develop in mediums containing high concentrations of streptomycin, while other cultures inoculated at the same time with lower concentrations have failed to show any growth at all. The occurrence of these "skips," "saltations," "paradoxic zones" or "inversions" suggests that the appearance of resistant forms is a chance phenomenon, revealed in large numbers of organisms by the inhibition of more susceptible ones but otherwise independent of the presence of streptomycin in the medium. Clinically, also, resistant forms cannot be prevented or delayed by heavy continuous treatment and do not appear earlier or more frequently with little or intermittent treatment.

COMBINED TREATMENTS

In the test tube, as well as in experimental animals, sulfones and other agents which have a weak antituberculous activity seem to combine with streptomycin to inhibit the growth of the organisms. Whether this is a true potentiation or synergism with increasing effect on combination or whether it is a mere additive or even partially additive effective is difficult to demonstrate. Sputum conversion or the disappearance of tubercle bacilli during streptomycin treatment is evidence of their susceptibility. When streptomycin treatment is combined with collapse therapy or other measures to control disease and stop the multiplication of the organisms, such sputum conversion occurs more frequently than when streptomycin alone is relied on. Patients now receiving treatment with combinations of streptomycin with collapse therapy, sulfones or other agents are being studied to see if they may be of clinical importance in delaying or preventing the appearance of resistant forms.

PATHOLOGIC STUDIES

Histologic examination of lesions which have responded to streptomycin treatment, both in animals and in human beings, shows pictures of regression, encapsulation and resorption or of persistence and progression similar to, though more frequent than, that encountered without streptomycin treatment. Most animal experiments have been performed with primary tuberculous infection, while most patients have been treated for lesions of the reinfection type. Results in a few animal experiments and a few children with primary infection who have been treated indicate, however, that the streptomycin is similarly effective in both forms.

Further experience has confirmed the emphasis on the location and age of the lesion rather than on immunologic character. Active tuberculous ulceration and granulations of the mucous membranes and draining sinuses from tuberculous lymph nodes or bones and joints have given the most strikingly uniform response. Recent acute miliary disseminations may fade away and tuberculous meningitis may show prolonged remissions, but recurrence or relapse and eventual failure are only too frequent. Fresh pulmonary exudates absorb rapidly and caseation encapsulates and shrinks, in experimental animals and in human beings, but the effects are too often incomplete. The lesions may recur or progress when the treatment is discontinued or the organisms become resistant. Fibrosis and cavitation resulting from destruction and replacement of pulmonary tissue are only symptomatically affected by the

treatment. The same is often true of renal and genital tuberculosis. Fistulas from tuberculosis of closed cavities in the body, as pleurocutaneous or bronchopleural fistulas in empyema, have also given disappointing results. With greater experience, physicians have become more conservative in assuming that a symptomatic response or apparent radiologic improvement will persist and have become more anxious to supplement streptomycin treatment by further surgical or chemotherapeutic measures.

SUMMARY

During the past year there has become available cheaper, purer and less toxic streptomycin, but it remains the only antibiotic of proved value in the treatment of tuberculosis. Its chemical identity has been established and chemical as well as biologic assay methods developed, but it has not yet been synthesized. It is absorbed only by parenteral routes, widely but not uniformly distributed in the body and excreted in the urine in a different manner than is penicillin. It appears to prevent multiplication without interfering with several other physiologic functions of tubercle bacilli, but the exact mechanism of its action is still obscure.

The blood levels after varying doses in different species of animals and in persons of different size have been studied. The minimal lethal doses and the toxic consequences of various doses and blood levels have revealed the limits of allowable dosage. Animal experiments and clinical experience have established the minimal effective daily dose that may be given. Smaller amounts given at greater intervals are safer and just as therapeutically valuable as the large amounts divided into frequent doses previously recommended.

Resistant forms of tubercle bacilli form the chief obstacle to its success. Combination of streptomycin with other forms of treatment, medical and surgical, offers at present the best hope of preventing the multiplication of these resistant forms. Indications for streptomycin have become more definite and its limitations are better appreciated, but much remains to be learned in order to utilize to the utmost this important advance in the treatment of tuberculosis.

ABSTRACT OF DISCUSSION

DR. ALLAN HURST, Denver: I would like to know whether Dr. Bogen has had any experience with the combination of streptomycin and promizole® (4,2'-diamino-diphenyl-5'-thiazole sulfone) as reported by Dr. Edith Lincoln. At the National Jewish Hospital, there is a patient who was treated at Bellevue Hospital and later reported as part of a series in the *Bulletin of the Johns Hopkins Hospital.* This girl of 15, with generalized tuberculosis, was reported successfully treated by a combination of promizole® and streptomycin. Since transfer to our institution evidence of renal tuberculosis has developed, with destructive changes in both kidneys, as well as joint manifestations. Treatment with promizole® is being continued at the request of Dr. Lincoln, but evidence has not been found that promizole,® alone or in combination with streptomycin, has been of any real value in this case.

DR. EMIL BOGEN: My only experience with promizole® has been limited to a few tests and experiments and a single patient. My co-workers and I have had somewhat more experimental experience with diasone,® and recently rather considerably with promin® (sodium p,-p'-diaminodiphenyl sulfone-N,N'-didextrose sulfonate) and similar diphenylsulfone agents. In the guinea pig, one can show slight retarding effects on tuberculosis from any of these agents; but none of them show anything comparable to the retardation shown by streptomycin alone. There does seem to be some increase in the effectiveness of streptomycin when it is combined with a diaminodiphenylsulfone agent. In renal involvement, we have had some rabbit experiments in which the combination seems much more effective on the inhibition of renal lesions, particularly when we had added promin® intravenously, which is rather rapidly excreted. We obtain rather high concentrations of this in the urine, sufficient to cause inhibition of tubercle bacilli, and this treatment, combined with streptomycin or given to patients who have already had organisms resistant to streptomycin after previous treatment for renal tuberculosis, has shown gratifying clinical results. In renal tuberculosis, particularly, in spite of the impressive results shown in the exhibit of the New York work of the Veterans Administration, our own experience has been that organisms are apt to recur following a period of treatment, and we feel that combined treatment in this particular instance is indicated.

CONSTRICTION OF THE INTERVERTEBRAL FORAMEN

A Cause of Nerve Root Pressure

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The intervertebral foramen, exit of the nerve root from the spinal canal, is limited in front by the intervertebral disk and portions of the adjacent vertebral bodies. Above and below are the pedicles, while posteriorly occur the superior and inferior articular processes, with the ligamentum flavum. This opening, which is the site of movement, is normally five or six times as large as the diameter of the nerve which passes through it, thus allowing a generous reserve cushion space. Nerve foramens, not the site of movement, are only slightly larger than the nerves which traverse

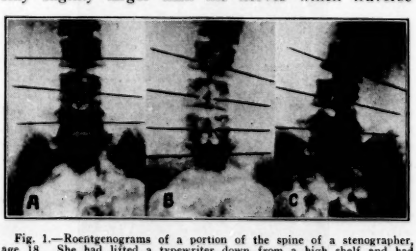

Fig. 1.—Roentgenograms of a portion of the spine of a stenographer, age 18. She had lifted a typewriter down from a high shelf and had experienced sudden pain down left leg. The transverse lines indicate the planes of the disk surfaces and relative sizes of the foramens (interpendunculate distances). *A*, bending to the left (painful side), the fourth lumbar foramen was maintained as large as possible. *B*, attempting to stand upright, with listing of the lumbar part of the spine away from the painful side. *C*, bending away from painful side, normal flexion. The disks are wedge shaped, thinner on the concave side. The diagnosis of fourth lumbar disk herniation was confirmed by operation.

them. In the spine this is noted in those cases of nonsegmentation in which adjacent vertebral segments remain congenitally fused. Here the foramen is much smaller, smooth in margin and usually round or slightly oval in shape.

Certain movements of the cervical and lumbar parts of the spine cause normal physiologic constriction of the foramen diameter. Dorsal extension and lateral flexion may decrease the diameter by as much as one third. In the cervical region, constriction also

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The Department of Anatomy and the Department of Pathology of the College of Medicine, Syracuse University, assisted in this study.

results from rotation. These facts may prove useful in eliciting or evaluating the patient's symptoms.

A radiograph of the lumbar part of the spine made with the patient standing at the full limit of lateral flexion will normally show the intervertebral disks wedge shaped, the narrow edge toward the concavity of the curve. In this anteroposterior view, the distance between the pedicles will be noted materially decreased on the side toward which the patient is bending.

In certain patients with symptoms of nerve root pressure, the upper and lower plane surfaces of the corresponding disk remain parallel. The foramen is not allowed to become smaller on lateral flexion toward the affected side, although normal wedging may take place at this level when the patient bends in the opposite direction (fig. 1). The adjacent disks may show normal wedging in both directions. Patients with limitation of movement from painful back conditions exhibit a more generalized restriction and absence of wedging.

In addition to the physiologic foramen constriction just described, encroachment on these openings may result from trauma, either fracture or dislocation.

So-called osteoarthritis is responsible for many cases of intervertebral foramen encroachment with consequent restriction of the reserve cushion space. This condition is not true arthritis but rather a noninflammatory degenerative process, more properly termed arthrosis or spondylosis. With this degeneration, thinning of the disk results, sclerosis of the vertebral body margins develops and the vertebral bodies come to lie more closely in contact. This approximates the pedicles decreasing the cephalocaudad diameter of the foramen.

Fig. 2.—Serial sections of a normal fifth lumbar disk, foramen and posterior articulation. The top is medial, the bottom is lateral.

Bony spur formation projects backward from the disk in front, or spur formation may project forward from the margin of the posterior articulation. The foramen becomes hour glass shaped.

Because of an incline to the plane of the posterior articulation, when the disk becomes thinned, the lower vertebra may become wedged forward—a reverse spondylolisthesis—decreasing the anteroposterior diameter of the foramen. Along with this subluxation, the upper tip of the lower articular process becomes thrust forward into the opening (fig. 4).

Fig. 3.—Spondylolisthesis; the fourth lumbar disk is forward on the fifth. Disk substance is bulging into the foramen, and the nerve is flattened into a thin ribbon-like structure.

There may be hyperplasia or ossification of the ligamentum flavum.

Examination of the lumbar region in cadaver material has frequently shown a bulging of disk substance backward and laterally into the foramen, especially at the levels of the fourth and fifth lumbar segments This may occur well out in the lateral portion of the opening. At this level the disk forms the lower anterior border of the foramen, so that bulging of disk substance displaces the nerve upward and backward against the unyielding uppermost pedicle. The nerve structure may become compressed, so that its normal oval shape is flattened or altered to the shape of a triangle (fig. 5), and fibrotic changes with adhesions may develop in and about the nerve where it passes through the foramen. In these circumstances, the usual relationship between the size of the nerve and the diameter of a movable opening through which it passes is no longer the normal of about 1 to 5 and the cushion space is lost.

It would seem from these cadaver studies that changes within the intervertebral foramen may frequently occur which are compatible with the clinical picture of nerve root pressure.

"Herniation of the intervertebral disk" has unfortunately come to be a popular diagnosis applied to the condition in patients with symptoms of nerve root pressure. Although the pressure may be at any point along the root, it is usually sought in the spinal canal, too often without success.

Williams and Yglesias[1] in 1933 advised "facetectomy" to enlarge the intervertebral foramen in patients with intractable sciatica. Gray[2] of London, after reporting 2 cases in which there were symptoms of nerve root pressure cured by posterior joint arthrectomy where no disk protrusion was found, remarked, "Evidently the intervertebral disc is not the only factor." This author, in treating 298 patients with sciatica, operated on 55 by arthrectomy for arthritis of the posterior joint. Twenty-five were cured. In this country, Briggs[3] has used arthrectomy to "decompress" the intervertebral foramen. The cadaver studies here reported would seem to confirm the logic of such an operation.

Gray, in reporting on the postoperative roentgenograms of 17 patients who had had disks removed, found narrowing of one or more disks; this had not been visualized in the preoperative roentgenograms in 10 of them. Thus resulted a late posterior joint subluxation and presumably foramen encroachment. He warned against curettage of the disk during operation for this reason, stating, "Only the part that is loose should be removed, and no more."

Certain authorities now condemn the use of contrast myelography as being unreliable and have stated that the neurologist should be able to diagnose nerve root pressure by his clinical examination without it. Radiographs in the standing-lateral-bending position, as well as careful roentgen studies of the foramens, should be of some assistance. If nerve root pressure occurs in the intervertebral foramen, it can hardly be visualized by contrast medium within the dural sheath, nor can it be cured by operation solely within the spinal canal.

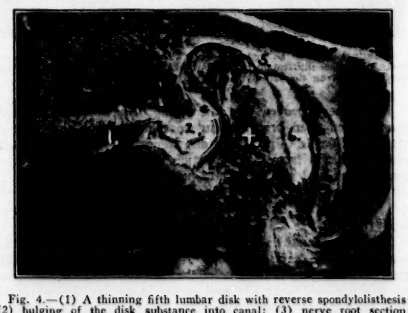


Fig. 4.—(1) A thinning fifth lumbar disk with reverse spondylolisthesis; (2) bulging of the disk substance into canal; (3) nerve root section; (4) subluxated articular process, encroaching on the foramen and impinging against the pedicle (5); posterior articular processes (6) do not register opposite each other. Perineural cushion space is almost completely absent.

Some patients will be relieved by rest alone, others by radiation applied to the nerve roots, while the most resistant cases may require operation. If operative intervention becomes necessary, not only the roomy spinal canal but the much smaller movable foramen must be investigated. This investigation must extend well out to the lateral side of the foramen structure. Decompression of the intervertebral foramen may be necessary.

Fig. 5.—Herniation of disk substance (1) into the intervertebral foramen compressing the fifth nerve root into triangular shape (2).

It would seem that these openings at the "crossroads" between the peripheral nervous system and the movable skeletal support merit much greater attention than they have received in the past.

1. Williams, P. C., and Yglesias, L.: Lumbosacral Facetectomy for Post Fusion Persistent Sciatica, J. Bone & Joint Surg. **15**: 579 (July) 1933.
2. Gray, C.: The Causes and Treatment of Sciatica Pain, Internat. Abstr. Surg. **85**: 417, 1947; in Surg., Gynec. & Obst., November, 1947.
3. Briggs, H., and Keats, S.: Laminectomy and Foraminotomy with Chip Fusion, J. Bone & Joint Surg. **29**: 328 (April) 1947.

ABSTRACT OF DISCUSSION

DR. L. H. GARLAND, San Francisco: The author's thesis bears the respectability of years, as well as the hearty concurrence of spinal manipulators at large—but I am not sure that either proves it. In his belief that foraminate changes are an established factor in many conditions diagnosed as nerve root pressure, Dr. Hadley makes several statements which bear review: (1) That the intervertebral foramen is normally five times the diameter of the corresponding nerve. Anatomically this applies only in the upper cervical and in the thoracic areas. In the lower cervical and the lumbar areas the nerves virtually fill their respective foramens, at least in most adult spines. (2) That degenerative spinal bone changes (arthrosis and spondylosis are bad terms) are often associated with intervertebral disk narrowing and subluxations of the posterior spinal articulations, with resultant nerve pressure. Clinically one sees many persons with hypertrophic spinal changes (including posterior osteophytes in the lower cervical area), thinned disks and articular offsets—and absolutely no symptoms. Therefore, it is difficult to believe that significant nerve pressure often results from such. (3) That reverse spondylolisthesis is an entity which may result in "thrusting forward an articular process into the foramen." This, I believe, is a rara avis—if existent at all. There is considerable trouble in assessing the relationship of the various posterior articular processes and the relative sizes of the intervertebral foramens in living persons. Roentgenograms (stereo-oblique) are simple to make but difficult to duplicate. Slight differences in positioning and in the projection of the central ray may cause decided variation in the roentgen shadows of these structures. "Reverse" olisthesis is often an illusion, produced by variation in contour of the posterior margins of adjacent vertebral bodies. Apparent sub-

luxations of articular facets (zygapophyseal joints) may also be secondary to positioning or technic. Both conditions (reverse slip and subluxation) do occur, but infrequently, and narrowed disks are not necessarily concomitant. Conversely, narrowed disks may be seen without grossly displaced facets, or evident foraminate narrowing. Therefore, I wonder whether the symptoms of nerve root pressure are not more likely to be due to soft tissue changes (degenerative, traumatic, etc.), rather than to alterations of foraminate shape or size. In either event, I believe that etiologic conclusions from roentgen studies are not always tenable. I would like to ask the author a few questions: (1) How many cadavers have been sectioned in these studies? (2) What percentage of compressed nerves secondary to articular subluxations were found? (3) Did review of the symptoms indicate good correlation?

DR. HENRY BRIGGS, East Orange, N. Y.: From operating and widely exposing foramens in over 100 patients and making explorations in many more, I am convinced that foraminate constriction is a common cause of back disability. Except in early stages, following a nuclear protrusion, foraminate constriction practically always follows some collapse of the intervertebral space. In teen ages the compression probably occurs after rupture of nuclear material into a vertebral body. As the bodies approximate, the disk bulges like a collapsing bellows and the ligamentum flavum thickens and bulges also. The disk bulge always carries out into the foramens in this group. In adults, after simple degeneration or degeneration with herniation, the same compression of the intervertebral space occurs and all the multiple manifestations described by Dr. Hadley follow. I have found all of them at operation, even a constriction that caused recurrent severe sciatica occurring seven years after a ruptured nucleus had been removed at the same level. The two common conditions that baffle me in operations on the low part of the back are the sucked back protrusions, called concealed disks, and the foraminate root oppressions. To determine the presence or absence of the first I have been in the habit of scraping the disk clean for inspection and palpation. To determine the latter adequately, part of the anterior surface of the inferior pedicle has to be removed by what I call an undermining foraminotomy. I am beginning to find evidence now that some of my explorations are followed by a late disk collapse. I wonder whether it is safe thoroughly to explore two and three disks in a search for pathologic changes. I find myself turning to the use of ethyl iodophenylundecylate (pantopaque®). As Dr. Hadley has pointed out, no contrast studies will solve the foraminate problem entirely, particularly at the lumbosacral level. Some of my best results have been in spines showing decided so-called hypertrophic arthritis, in which I have performed a wide opening of one or more foramens by adding to an arthrectomy a removal of part of the pedicles to their bases, doing what I call a complete foraminotomy. My guide for these operations has been disk collapse as shown on the lateral roentgenograms.

DR. LEE A. HADLEY, Syracuse, N. Y.: I wish to thank the men who have discussed my paper. Relative to Dr. Garland's question, I have been interested in studying the cadaver spines for the past eighteen years. I am sorry to have given Dr. Garland the idea that I feel that the spur, by itself, causes symptoms. Of course, one must differentiate between a harmless spur that projects laterally from the vertebral body and one that projects backward into the foramen. Many patients with spurs projecting into the foramen do not have symptoms. That condition, however, decreases or eliminates the normal protective reserve cushion space around the nerve. When the patient with such a condition inadvertently steps off a curb or gets a "snap the whip" effect to his neck from an automobile collision, he is likely to have nerve root pressure symptoms. Charles Gray, in *Surgery, Gynecology and Obstetrics* for November 1947, published an excellent article on this subject. It bears out some of the conclusions which I have enumerated, although his point of view was that of the surgeon. One cannot disregard the fact that in many cadavers, the nerve root is found to be definitely compressed into an abnormal shape by the surrounding structures.

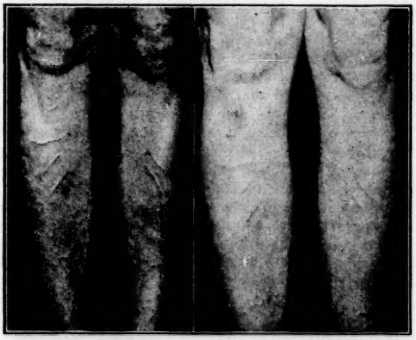
Clinical Notes, Suggestions and New Instruments

AN EARLY SIGN OF FEMORAL THROMBOSIS

GERALD H. PRATT, M.D.
New York

The early diagnosis of thrombosis of the deep veins of the legs is one of the most difficult, as well as most important diagnoses doctors have to make. The condition, frequently, is unsuspected until embolism occurs. This missed diagnosis may cause a serious or a fatal complication. While surgical or anticoagulant therapy, or a combination of the two, can reduce effectively these complications, the diagnosis must be made first.

In a previous report on the diagnosis and treatment of thrombosis of the deep veins of the leg, I briefly mentioned the presence of three dilated veins over the tibia as an early sign.[1] Since then, this phenomenon has been observed so consistently that the term "sentinal" veins has been coined for it. I believe that these veins are the earliest objective sign of deep vein thrombosis and that attention should be directed to their presence so that effective therapy can be started. I have observed this sign early in over 80 per cent of the patients with pathologic clotting.



"Sentinal veins. Dilated veins over the tibia, an early sign of thrombosis. In the illustration on the right, the process on the right leg preceded that on the left by two days.

It has been proved that the thrombosis which causes pulmonary embolism originates in most instances in the veins of the calf (Roessle,[2] Frykholm[3] and Neumann[4]). This pathologic clotting results from a combination of factors, of which three are fundamental and constantly present. These three are: (1) an abnormal change in the blood clotting factor in the patient, (2) stasis of the blood flow and (3) endothelial irritation or injury.

The stasis and endothelial irritation may result from the trauma on the veins from bed rest alone. The clotting and thrombosis begin in the veins of the calf muscles and progresses to the popliteal vein. It propagates along the lining of the vein wall before occluding it. The first veins to dilate due to this obstruction are the ones opening directly into the popliteal vein, particularly branches of the anterior tibial vein. The collateral vessels are sufficiently abundant so that dilatation of the main veins with edema occurs very late, actually when the clotting has progressed to completely occlude the popliteal vein lumen. At such time, either embolism occurs or the obstruction is complete and edema results. These three small veins over

From the Vascular Clinic of St. Vincents Hospital, New York, and New York University.

1. Pratt, G. H.: S. Clin. North America **28**: 341, 1948.
2. Roessle, R.: Virchows Arch. f. path. Anat. **300**: 180, 1937.
3. Frykholm, R.: Surg., Gynec. & Obst. **71**: 307, 1940.
4. Neumann, R.: Virchows Arch. f. path. Anat. **301**: 708, 1938.

the tibia empty into the saphenous and the anterior tibial vein system, are superficial and unsupported by musculature and therefore dilate very early.

This sign was present 84 times in 109 instances of thrombosis and lead to the early diagnosis. It is an earlier sign than the so-called Homans[5] sign. It is caused only by thrombosis, while the Homans sign may be positive in the presence of any inflammation of the skin or soft tissues in addition to a thrombosis.

This sign joins the other early diagnostic points which I have reported after studying 90 cases of fatal embolism and several hundred of nonfatal thrombosis.[6] These signs are: (1) pain in the popliteal space or calf, (2) tenderness over the involved vein areas, (3) slight cyanosis of the part compared to the other one, (4) abnormally elevated pulse rate and temperature, (5) fear of impending disaster (many patients are aware that something is wrong), (6) very mild edema, (7) a small nonfatal embolism (25 per cent of the patients have a small embolism before a fatal one) and (8) "sentinal" veins as described.

Since most of these signs are subjective, an objective sign will be helpful in earlier diagnosis and treatment of this increasingly important syndrome.

Council on Pharmacy and Chemistry

NEW AND NONOFFICIAL REMEDIES

The following additional articles have been accepted as conforming to the rules of the Council on Pharmacy and Chemistry of the American Medical Association for admission to New and Nonofficial Remedies. A copy of the rules on which the Council bases its action will be sent on application.

AUSTIN SMITH, M.D., *Secretary.*

METHENAMINE-U. S. P. (See New and Nonofficial Remedies 1948, p. 122).

The following dosage form has been accepted:

THE WARREN-TEED PRODUCTS COMPANY, COLUMBUS 8, OHIO

Tablets Methenamine: 0.3 Gm. and 0.5 Gm.

METHADONE HYDROCHLORIDE (See New and Nonofficial Remedies 1948, p. 25).

The following additional dosage form has been accepted:

ABBOTT LABORATORIES, NORTH CHICAGO, ILL.

Syrup Methadone Hydrochloride: 1.25 mg. per 4 cc., 473 cc. and 3.78 liter bottles.

METHIONINE (See THE JOURNAL, Oct. 9, 1948, p. 430).

The following dosage form has been accepted:

WALKER VITAMIN PRODUCTS, INC., MOUNT VERNON, N. Y.

Capsules Methionine: 500 mg.

GOLD AND SODIUM THIOSULFATE-N. F. (See New and Nonofficial Remedies 1948, p. 524).

The following dosage form has been accepted:

E. S. MILLER LABORATORIES, INC., LOS ANGELES 14

Solution Gold Sodium Thiosulfate: 25 mg. and 50 mg. Flacons.

OXIDIZED CELLULOSE (See New and Nonofficial Remedies 1948, p. 432).

The following additional dosage form has been accepted:

JOHNSON & JOHNSON, NEW BRUNSWICK, N. J.

Hemo-Pak Absorbable Gauze Packing Strip (4 ply): ½" x 5" (1.27 by 12.70 cm.) in sealed tube.

U. S. patents 1,939,235 and 2,232,990.

5. Homans, J.: New England J. Med. **235:** 163 and 193, 1946.
6. Pratt, G. H.: New York State J. Med. **46:** 1825, 1946. Footnote 1.

Council on Foods and Nutrition

The following water-packed fruits have been accepted as conforming to the Rules of the Council.

JAMES R. WILSON, M.D., *Secretary.*

The Pratt-Low Preserving Company, Santa Clara, Calif.

PRATTLOW BRAND YELLOW CLING PEACHES consists of the fruit itself, packed in water without any added sugar or salt.

Analysis (submitted by manufacturer).—Moisture 91.9 per cent, ash 0.3 per cent, fat (ether extract) 0.1 per cent, protein (N × 6.25) 0.4 per cent, crude fiber 0.3 per cent, carbohydrates (by difference) 7.0 per cent, ascorbic acid 3.9 mg. per hundred grams.

Calories.—0.31 per gram; 8.8 per ounce.

Use.—For use in diets of patients on restricted sugar intake.

PRATTLOW BRAND BARTLETT PEARS consists of the fruit itself, packed in water without any added sugar or salt.

Analysis (submitted by manufacturer).—Moisture 91.1 per cent, ash 0.2 per cent, fat (ether extract) 0.1 per cent, protein (N × 6.25) 0.2 per cent, crude fiber 0.6 per cent, carbohydrates (by difference) 7.8 per cent, ascorbic acid 1.5 mg. per hundred grams.

Calories.—0.33 per gram; 9.4 per ounce.

Use.—For use in diets of patients on restricted sugar intake.

PRATTLOW BRAND UNPEELED APRICOT HALVES consists of the fruit itself, packed in water without any added sugar or salt.

Analysis (submitted by manufacturer).—Moisture 91.8 per cent, ash 0.4 per cent, fat (ether extract) 0.1 per cent, protein (N × 6.25) 0.5 per cent, crude fiber 0.3 per cent, carbohydrates (by difference) 6.9 per cent, ascorbic acid 3.9 mg. per hundred grams.

Calories.—0.31 per gram; 8.8 per ounce.

Use.—For use in diets of patients on restricted sugar intake.

PRATTLOW BRAND FRUIT COCKTAIL, consisting for the most part of pears, peaches and pineapple with some grapes and maraschino type cherries, is packed in water without any added sugar or salt.

Analysis (submitted by manufacturer).—Moisture 89.0 per cent, ash 0.3 per cent, fat (ether extract) 0.1 per cent, protein (N × 6.25) 0.4 per cent, crude fiber 0.4 per cent, carbohydrates (by difference) 9.8 per cent.

Calories.—0.42 per gram; 11.9 per ounce.

Use.—For use in diets of patients on restricted sugar intake.

PRATTLOW BRAND KADOTA FIGS consists of the fruit itself, packed in water without any added sugar or salt.

Analysis (submitted by manufacturer).—Moisture 87.4 per cent, ash 0.4 per cent, fat (ether extract) 0.1 per cent, protein (N × 6.25) 0.5 per cent, crude fiber 0.8 per cent, carbohydrates (by difference) 10.8 per cent.

Calories.—0.46 per gram; 13.0 per ounce.

Use.—For use in diets of patients on restricted sugar intake.

The following products have been accepted as conforming to the Rules of the Council.

JAMES R. WILSON, M.D., *Secretary.*

Maple Island Farm, Inc., Stillwater, Minn.

MIF INFANT FOOD consists of fresh, clean pasteurized milk, corn syrup solids, ferrous gluconate, vitamin A, vitamin D, thiamine hydrochloride, niacinamide and ascorbic acid.

Analysis (submitted by manufacturer).—Milk fat 21.0 per cent, milk proteins (N × 6.38) 23.0 per cent, lactose 32.0 per cent, dextrins, glucose and maltose, 17.0 per cent, ash, 5.0 per cent, moisture 2.0 per cent.

Calories.—4.75 per gram; 135.00 per ounce.

Vitamins and Minerals.—

	Per Hundred Grams
Vitamin A	2,600.00 U.S.P. units
Vitamin D	700.00 U.S.P. units
Thiamine Hydrochloride	0.65 mg.
Riboflavin	1.00 mg.
Niacinamide	6.50 mg.
Ascorbic acid	26.00 mg.
Calcium	750.00 mg.
Phosphorus	500.00 mg.
Iron	5.00 mg.

Use.—For infant feeding.

The Lynne Corporation, Oakland, Calif.

LYNNE BRAND DEHYDRATED GOAT'S MILK, a spray-dried, homogenized whole goat's milk.

Analysis (submitted by manufacturer).—Water 2.0 per cent, total solids 98.0 per cent, ash 6.5 per cent, fat 27.0 per cent, protein (N × 6.38) 26.5 per cent, lactose (by difference) 38.0 per cent.

Calories.—5.0 per gram; 142.0 per ounce.

Use.—As a replacement for cow's milk in special diets.

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SATURDAY, JUNE 4, 1949

THE GROWTH OF MEDICAL GROUP PRACTICE

A study of group practice, begun by Dr. G. Halsey Hunt and Dr. Marcus Goldstein in 1946, has been reported in two articles in THE JOURNAL and in a more recent communication on the growth of groups published elsewhere.[1]

The purpose of the study is thus stated:

> An estimation of the stability of this form of medical practice (group practice) therefore should be of specific interest. The present report attempts such an estimation based on longevity and growth in staff members of a fairly large proportion of existing groups.

The sample from which Dr. Goldstein's information was derived was 98 medical groups in existence during 1947. The field work was conducted by members of the United States Public Health Service on routine duty who visited certain selected groups along their route of travel. These 98 groups include more than one fourth of the 368 groups listed by Hunt in the 1946 survey.[2]

These 98 existing groups are examined with respect to the relationships between size and age of groups, size of community in which the groups are located, increase in the size of the groups from the date of inception, and physician "turnover." The data reaffirm previous results.[3] The largest number of groups are found in communities of less than 10,000; the groups in the larger population centers tend to have more members. Dr. Goldstein finds that the mean age of 98 existing groups is 19.9 years; most of them retain the majority of their original members and 82 per cent of these groups have increased in size since their beginning.

By "stability" the survey apparently attempts to measure the success and popularity among physicians of group organization as a method of practicing medicine. If several organizations of a certain type for practicing medicine (groups) have been in existence for some time and have lost few members for causes other than death, the investigator assumes that the stability of this type of organization has been demonstrated. This study cannot, however, be considered a definitive study of the mortality or stability of groups but must rather be considered as merely a study of surviving groups in 1947. Examination of the successes supplies no information on the failures and thus on the stability of group practice as a whole. Knowing only the numbers who survived through a given span of years, an actuary cannot establish a mortality table; he must know also the original number alive at the beginning of the period. Only the strong survive in nature, and this is probably true also for group practice.

At the beginning of his article Dr. Goldstein notes that an examination of disbanded groups would be necessary for a complete discussion of the growth of medical groups. His conclusion limits the evidence of stability to "many instances."

This study contributes to our knowledge of medical groups, but should be read in its true setting as an interesting, retrospective study of existing groups. The paper also throws some light on medical vacancies among groups that should be of interest to physicians beginning practice. Some 42 of the examined groups are planning to increase their staffs; otolaryngologic specialists are in most demand and general practitioners the least.

1. Hunt, G. H.: Medical Group Practice in the United States: III. Report of a Questionnaire Survey of All Listed Groups, 1946, J. A. M. A. **135**: 904-909 (Dec. 6) 1947. Goldstein, M. S.: Medical Group Practice in the United States; IV. Organization and Administrative Practices, J. A. M. A. **136**: 857-861 (March 27) 1948; Medical Group Practice in the United States: V. Growth of Groups, Journal Lancet **69**: 42-46 (Feb.) 1949.
2. Hunt, G. H.: Medical Groups in the United States, 1946, U. S. Public Health Service, Division of Public Health Methods, February 1947.
3. Group Medical Practice, Bureau of Medical Economics, Chicago, American Medical Association, 1940, p. 24.

STREPTOMYCIN

In 1944, Herrell reported that "a rather striking suppressive effect on the course of tuberculosis of guinea pigs was obtained" by treating the animals with streptomycin at varying intervals. As nearly as arbitrary numerals could express it, the tuberculosis index of infection controls was 81.9 as compared with 2.8 for the treated.[1] At the time streptomycin was said to have a suppressive effect on human tuberculosis infection in guinea pigs in addition to being well tolerated by the animals. However, not all early students were so enthusiastic.[2] In the fall of 1946 and after it had been demonstrated that streptomycin had definite therapeutic potentialities in the treatment of clinical tuberculosis, large quantities of streptomycin became available for clinical tests. Such tests were urgent because of the numerous reports of cures and for the purpose

1. Herrell, W. E.: Penicillin and Other Antibiotic Agents, Philadelphia, W. B. Saunders Co., 1945, pp. 317-318.
2. Corper, H. J., and Cohn, M. L.: The Tubercle Bacillus and Fundamental Chemotherapeutic and Antibiotic Action, Yale J. Biol. & Med. **19**: 1-22, 1946.

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of determining (1) the types of pulmonary tuberculosis most likely to benefit from the use of streptomycin; (2) the most satisfactory methods and frequency of treatment; (3) the optimum daily dosage; (4) the optimum duration of treatment; (5) the most timely integration of streptomycin with other therapeutic procedures; (6) the significance of less sensitive strains to the drug; (7) the significance of serious toxic manifestations, and (8) relapse of the disease.

Results in summary form[3] are now available on 332 patients with pulmonary tuberculosis treated with streptomycin. The degree of therapeutic efficiency of streptomycin is definitely related to the character of the pulmonary disease, with improvement greater in predominantly acute disease than in predominantly chronic disease. As the progression of chronic tuberculosis is fundamentally related to the occurrence of acute episodes, the great potentialities of the strategic use of short courses of streptomycin to combat such episodes should be stressed. Larger doses of streptomycin appeared to be favored over smaller daily doses, but this advantage was often minimized or nullified by severe toxic manifestations incident to larger dosage. Hope is placed in the future use of dihydrostreptomycin to solve this. However, many of the questions poised in 1946 are still unanswered. The "drug fastness" is unquestionably a significant factor in limiting the effectiveness of the antibiotic streptomycin. The phenomenon appears to be common to both streptomycin and dihydrostreptomycin.[4] Significantly, the failure to close cavities and suppress sputum in a larger percentage of patients and the relapse of the disease with increasing frequency after time has elapsed suggest the limitations of this antibacterial therapy for this characteristically chronic disease. The absolute necessity of using more definitive treatment, notably collapse therapy, to obtain more lasting results is emphasized also.

Even after such enormous amounts of clinical data have been accumulated many of the questions regarding the exact mechanism of action of streptomycin in vitro and in vivo remains a mystery. Although it now appears that streptomycin and allied antibiotics are beneficial agents in pulmonary tuberculosis in only definitely defined conditions and periods of infection, and then only within the limitations of "drug fastness," a wholehearted and serious effort should be made to determine the mechanism of action of streptomycin in tuberculosis. In this way and this way only will its inadequacies be overcome and a better understanding of tuberculosis itself ensue. Review of the history of chemotherapy in tuberculosis is disheartening. Tuberculosis is still a disease of major significance, and sanatoriums are still necessary.

3. Riggins, H. M., and Hinshaw, H. C.: Streptomycin-Tuberculosis Research Project of the American Trudeau Society, Am. Rev. Tuberc. **59**: 140-167, 1949.

4. Feldman, W. H.; Karlson, A. G., and Hinshaw, H. C.: Dihydrostreptomycin: Its Effect on Experimental Tuberculosis, Am. Rev. Tuberc. **58**: 494-500, 1948.

TONSILLECTOMY DURING EPIDEMIC POLIOMYELITIS

THE JOURNAL,[1] March 21, 1942, warned that poliomyelitis, particularly the bulbar form, greatly increased in children after tonsillectomy or adenoidectomy in epidemic areas. Reports of Stillerman, Fischer, Maxwell, Marks, Top, Aycock and Sabin were cited. Since that time avoidance of such operations during epidemics has been almost universally adopted. Recently, otolaryngologists seem inclined to the belief that a causal relationship does not exist between the two and that bulbar poliomyelitis following tonsillectomy is probably purely coincidental. Cunning,[2] as a result of a survey conducted at the request of the American Laryngological, Rhinological and Otological Society, based on questionnaire survey data covering 1947, felt that the operation should not be indefinitely postponed simply because summer months are the months that poliomyelitis is prevalent. Cunning's report and other factual material relating to this question were recently reviewed by Faber.[3] Data on 4,331 cases of poliomyelitis occurring in twenty-five states during 1947 which had been reported by Cunning were reexamined. Incidence of the bulbar type of poliomyelitis was noted to be 25 per cent in the group who had been subjected to tonsillectomy within two months of onset. Incidence of the bulbar type in the entire group was 11.7 per cent. Corresponding figures for 1946 showed an incidence of 29 per cent bulbar type of poliomyelitis among the post-tonsillectomy cases as compared with 15.4 per cent of the bulbar type in the entire group. Thus the incidence of cases of bulbar type was more than twice as great in patients who had been subjected to tonsillectomy as in those who had not been. A previous statistical study by Anderson[4] of poliomyelitis in Utah in 1943 showed incidence of cases of bulbar type in the general child population to be 25 per 100,000 as compared with 404 per 100,000 in children who had recently had tonsillectomies. Faber concluded that proofs previously offered for a causal relationship between incidence of poliomyelitis and tonsillectomy during epidemic times were still valid and that evidence for this had not been refuted by the Cunning survey.

The weight of past and recent evidence favors the existence of such a relationship. As tonsillectomy is an elective operation which rarely requires immediate surgical attention, the preventive attitude of delay is justified. Until conclusive evidence is presented that such procedures do not increase incidence of poliomyelitis the inadvisability of operation during periods of epidemic poliomyelitis should be emphasized.

1. Tonsillectomy and Poliomyelitis, editorial, J. A. M. A. **118**: 980 (March 21) 1942.

2. Cunning, D. S.: Tonsillectomy and Poliomyelitis, Arch. Otolaryng. **46**: 575 (Nov.) 1947; Tonsillectomy-Poliomyelitis Survey, Laryngoscope **58**: 503 (June) 1948.

3. Faber, H. K.: Adenotonsillectomy and Poliomyelitis, Pediatrics **2**: 255 (Feb.) 1949.

4. Anderson, J. A.: Poliomyelitis and Recent Tonsillectomy, J. Pediat. **27**: 68 (July) 1945.

Current Comment

MULTIPLE SCLEROSIS SURVEY

The National Multiple Sclerosis Society announces a statistical research on the prevalence and geographic, climatologic and racial characteristics of multiple sclerosis. Dr. Leonard Kurland, epidemiologic statistician of the United States Public Health Service, is directing the survey in the field. Already New Orleans has been surveyed, and surveys are in process in San Francisco and in Denver. The society anticipates that the complete survey will require about a year for completion. Announcements are being made from radio stations concerning the survey with the hope that known cases will be reported to the National Multiple Sclerosis Society, 270 Park Avenue, New York City, giving the name of the patient. This plan has been endorsed by several official agencies.

REGISTRATION UNDER THE HARRISON NARCOTIC ACT

Physicians who are registered under the Harrison Narcotic Act or under the Marihuana Tax Act must effect registration on or before July 1 to avoid a penalty. Each year, despite the annual warnings in THE JOURNAL, this requirement is overlooked by some physicians and unpleasant consequences follow. Failure to register adds a penalty of 25 per cent to the tax payable and in addition subjects the physician to the possibility of a fine not exceeding $2,000 or imprisonment for not exceeding five years, or both. As an act of grace the Commissioner of Internal Revenue has in past years given some tardy registrants the choice between paying sums by way of compromise, a procedure authorized by law, or accepting criminal prosecution. If this procedure does not produce the required promptness in reregistration, the commissioner will have no other alternative than to institute criminal prosecution.

THE RUTGERS INSTITUTE OF MICROBIOLOGY

Dr. Robert C. Clothier, president of Rutgers University, has announced that the University will establish an Institute of Microbiology costing approximately $1,000,000. Dr. Selman A. Waksman will be its first director. Funds for a $1,000,000 building to house the institute and a grant of $250,000 toward its operating expenses will come from royalties on the streptomycin patent. Operating income will be provided in part by the royalties, with University funds and grants from private sources making up the remainder. Dr. Waksman, an alumnus of Rutgers and a member of its staff for more than twenty-five years, assigned his patent to the Rutgers Research and Endowment Foundation with the understanding that any net profits would be used to further research, particularly in microbiology. The new institute will not only give Dr. Waksman and his associates greatly increased facilities for expanding research in microbiology but will make possible an increased program of graduate teaching to insure a supply of young men and women trained to carry on this work. Establishment of the new Institute of Microbiology as a major branch of the state university will, according to Dr. Clothier, permit a full scale exploration of the potentialities of micro-organisms as instruments for human betterment. Equally important with the fundamental and applied research will be instruction at the graduate level so that greater numbers of future scientists can benefit from the learning and experience of Dr. Waksman. Dr. Waksman's decision to place the proceeds from the royalties accruing from his discoveries into further scientific research is another measure of the stature of this outstanding scientist. Streptomycin, the antibiotic drug which provided the long-sought treatment for many forms of tuberculosis, influenza meningitis, cholera, plague, stubborn urinary and blood infections, certain intestinal infections and undulant fever, was patented by Dr. Waksman in 1945. This and eight other Waksman patents have been assigned to the Research and Endowment Foundation. "Evidence is accumulating," states Dr. Waksman, "that we have but scratched the surface of the potentialities of microbiology, not only in medicine, but in agriculture, industry and all other fields of human endeavor."

AMPHETAMINE INTOXICATION

Popular attention has again been directed by radio commentators and others to the fact that benzedrine® has been used by prisoners as a means of stimulation. Since benzedrine,® or amphetamine, is the chief ingredient of inhaling devices widely used in the United States, access to the product is not difficult. Actually a Congressman has prepared a bill suggesting that amphetamine be placed on the narcotic list, although the drug is not in any sense a narcotic, nor is there any evidence that it is addictive. The persons who use amphetamine are apparently those who try all sorts of drugs as stimulants of sensation, including alcohol, marihuana and bromides as well as the usual narcotic preparations. The prisoners who use amphetamine usually open the inhaler and remove the filler. When the filler is soaked in alcohol or water, the drug passes into solution, and if the entire contents of an inhaler are taken at one time, definite stimulation results. Recently evidence became available that women were smuggling the drug into certain prisons. The effects of the stimulation are manifest in irritability; prisoners start fights and even riots, and may resort to sexual attacks. Some newspapers have referred to the use of the product by the "teen agers," who in some instances have dropped the fillers into carbonated or alcoholic drinks with the hope that the stimulus resulting will enable them to perform more efficiently in the more excitable forms of dancing—such as "jitterbug," "cut a rug" and what not! Indeed among the "teen agers" this form of stimulation is now known as a "bene jag." The lives of those responsible for the control of the drugs seem to be a continuous succession of attempts to meet new problems resulting from the unwarranted use of drugs for purposes unrelated to medicine.

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ORGANIZATION SECTION

Official Notes

ESTABLISH NATIONAL COMMISSION ON CHRONIC ILLNESS

A National Commission on Chronic Illness was formally launched May 20 at a luncheon meeting in Chicago, at which time Mr. Leonard W. Mayo, Cleveland, vice president of Western Reserve University, was installed as chairman of the commission. The speaker at the luncheon was Dr. Leonard A. Scheele, Surgeon General of the U. S. Public Health Service, whose subject was "The Turning Point in Our Care of the Chronically Ill."

The commission is an outgrowth of the Joint Committee on Chronic Disease, set up in 1946 through the cooperative efforts of the American Hospital Association, the American Medical Association, the American Public Welfare Association and the American Public Health Association. In May 1948 the National Health Assembly, held in Washington, D. C., recommended that the Joint Committee on Chronic Disease be expanded to a national commission, with increased membership, backing and responsibilities. The joint committee constituted itself a National Interim Commission on Chronic Illness, under the chairmanship of Dr. James R. Miller of Hartford, Conn., who, as a representative of the American Medical Association, was one of the original members of the Joint Committee on Chronic Disease.

Office space for the commission is being provided by the American Medical Association, which, with other voluntary health and medical organizations, is supporting the commission's work by a financial contribution. The members of the interim commission representing the four national professional organizations remain as members of the permanent body. They are, in addition to Dr. Miller, who becomes vice chairman of the permanent commission: J. Douglas Colman and Dr. Albert A. Snoke, representing the American Hospital Association; Dr. Thomas A. McGoldrick, representing the American Medical Association; Drs. Dean W. Roberts and Edward S. Rogers, representing the American Public Health Association, and Dr. Ellen C. Potter and Judge Thomas S. Waxter, representing the American Public Welfare Association.

The Commission will have thirty members, all of whom will serve without remuneration. They include prominent citizens from all parts of the country, representing the broad fields of industry, medicine, education, labor, farming, religion, public health and hospital administration, as well as the general public. Among them are: S. Bruce Black, president of the Liberty Mutual Insurance Company, Boston; Miss Sarah Blanding, president of Vassar College; Joseph W. Fichter, Master of the Ohio State Grange; Walter Reuther, president of the United Auto Workers, C. I. O.; Dr. Thomas Parran, dean of the Graduate School of Public Health, University of Pittsburgh; Dr. Ward Darley, dean of the School of Medicine, University of Colorado; Karl P. Meister, Executive Secretary, Board of Hospitals and Homes of the Methodist Church, and Mrs. Joseph T. Ryerson of Chicago.

The commission will have expert counsel and guidance from a group of thirty-two technical advisors, selected on the basis of their accomplishments in the five fields which will be most pertinent to the commission's work: clinical problems (including prevention and research); institutional care (including hospitals and nursing homes); noninstitutional care; rehabilitation and convalescence, and community problems. The technical advisors held all day meetings to draw up a program of objectives for the new commission. Chairmen for these group meetings were Dr. Ernst Boas, New York; Dr. Jack Masur, National Institutes of Health, Bethesda, Md.; Dr. Martin Cherkasky, New York; Dr. Howard Rusk, New York, and Dr. Lester Breslow, chief of the Chronic Disease Division, California State Department of Health.

SEVEN STATES NOW

Three more states have recently joined the parade of state legislatures which have petitioned the United States Congress not to pass legislation providing for compulsory health insurance. This makes a total of seven states to date expressing objection from one or both houses to the federalization of medicine. The latest state legislatures to act are Michigan, Florida and Maryland. The Delaware legislature passed such legislation, but it was vetoed by the Governor.

Washington Letter

(From Our Regular Correspondent)

May 30, 1949.

Compulsory Insurance Chief Issue as Hearings Open

Some of the nation's leading opponents and defenders of national compulsory health insurance testified before Senate and House committees during the first week of hearings on the Taft, Hill and Thomas-Murray-Dingell bills. The House hearings have been recessed until June 7, but those under way in the Senate are being continued until the week of June 13, when there will be a one week hiatus.

Senate committee witnesses in the first week, beginning May 23, included J. Donald Kingsley, Assistant Federal Security Administrator; Senators Taft and Hill; Dr. Louis H. Bauer, for the American Medical Association; Dr. Lowell S. Goin, California Physicians' Service; Dr. Carl O. Flagstad, American Dental Association, and Seymour E. Harris, Americans for Democratic Action.

Among those who appeared before the House committee, whose hearings opened on May 20, were Dr. R. L. Sensenich, American Medical Association; Dr. Channing Frothingham and Albert D. Lasker, Committee for the Nation's Health; Dr. Flagstad and Mr. Kingsley.

Public attendance was large at both hearings. Senator James E. Murray (Democrat, Montana) and Representative J. Percy Priest (Democrat, Tennessee) presided over the respective sessions.

Dr. Bauer described the Thomas-Murray-Dingell plan (S. 1679) as "an extreme example of compulsory paternalism, wrong in principle, impossible of practical operation and contrary to our established ways and habits of life and political principles." With reference to the supply of physicians, he observed that medical education does not present an acute problem and it can take care of the needs without government intervention.

Dr. Sensenich, whose direct statement was substantially the same as that presented on the other side of the Capitol by Dr. Bauer, underwent intensive questioning by members of the Priest committee, particularly Representatives Sadowski (Democrat, Michigan), O'Hara (Republican, Minnesota), Biemiller (Democrat, Wisconsin) and Wilson (Democrat, Oklahoma). In the course of interrogation, Dr. Sensenich brought out the following points: Adoption of the American Medical Association policy on government aid to medical schools is in abeyance pending outcome of current investigations on the subject; passage of the National Science Foundation bill is favored by the American Medical Association; insinuations that the American Medical Association is attempting to hold down the number of medical students in this country are without foundation in fact.

Dr. Goin, in his testimony, struck back at accusations made against the American Medical Association's educational campaign, especially by Representative Dingell (Democrat, Michigan) in the statement which he read to the Priest committee on the opening day (May 20) of the hearing.

"The American Medical Association—openly, frankly and honestly—is engaged in a National Education Campaign to give

the people the facts about compulsory health insurance and the facts about voluntary health insurance," he said. "We frankly oppose the first and we enthusiastically favor the second. We hope and believe that the American people, given the facts, will agree with us."

If this campaign, he added, is lobbying, then "it is lobbying in the finest American tradition and every doctor is proud of his part in the program."

Testimony in support of compulsory health insurance legislation was offered by Dr. Frothingham, Mr. Lasker, Mr. Kingsley and Professor Harris, who is professor of economics at Harvard.

Support of the various national health bills they are co-sponsoring was presented to the Murray committee by Senators Taft (S. 1581), Hill (S. 1456) and Thomas (S. 1679). "There is no question that S. 1679 would lead to nationalization and socialization of medicine," Senator Taft stated under a brisk interrogation by Senator Humphrey, a co-sponsor of that measure.

Antibiotic Certification Bill Advances

The House on May 16 passed H. R. 3151, which would add aureomycin, bacitracin and chloramphenicol to the list of drugs which must undergo federal inspection before distribution. On the same day, a companion bill (S. 1867) was introduced in the Senate to expedite consideration in that branch of Congress of the proposed amendment to the Federal Food, Drug and Cosmetic Act of June 25, 1938. Under present law, samples from every batch of insulin, streptomycin and penicillin manufactured for sale must be tested in Washington laboratories of the Food and Drug Administration prior to release in trade channels. The new legislation, if enacted and approved by the President, will make aureomycin, bacitracin and chloramphenicol (chloromycetin®) subject to the same controls.

Health Assembly Report Due In July

July 13 is the tentative publication date for "America's Health: A Report to the Nation," the official résumé of the National Health Assembly held in Washington in May 1948. The volume, containing some 400 pages, will carry findings and recommendations of each of the fourteen professional sections into which the assembly was divided. In addition, there will be a chapter on international cooperation for protection and promotion of public health. The book is being published by Harper's, and its price is expected to be $4.50. Special discounts will be granted on quantity orders, as well as orders by accredited delegates to the Assembly.

Bureaucracy "Out of Control," Says Sen. Byrd

"It appears that the bureaucracy is out of control with respect to personnel and drastic action is necessary," Senator Harry F. Byrd (Democrat, Virginia) warned on May 19. The senior senator from Virginia, one of the foremost Democratic opponents of compulsory health insurance, asserted that the federal payroll has increased by 146,541 employees since January 1948.

Coming Medical Meetings

American Medical Association, Atlantic City, June 6-10. Dr. George F. Lull, 535 N. Dearborn St., Chicago 10, Secretary.

American Association of Railway Surgeons, Chicago, Drake Hotel, June 30-July 2. Dr. Chester C. Guy, 5800 Stony Island Ave., Chicago 37, Secretary.

American Neurological Association, Atlantic City, Chalfonte-Haddon Hall, June 13-15. Dr. H. Houston Merritt, 710 W. 168th St., New York 32, Secretary.

Idaho State Medical Association, Sun Valley, June 20-23. Dr. Alfred M. Popma, 220 N. First St., Boise, Secretary.

Maine Medical Association, Poland Spring, Poland Spring House, June 19-21. Dr. Frederick R. Carter, 142 High St., Portland 3, Secretary.

New Hampshire Medical Society, Newcastle, Hotel Wentworth, June 14-15. Dr. Carleton R. Metcalf, 5 S. State St., Concord, Secretary.

Society for Investigative Dermatology, Atlantic City, Ritz Carlton Hotel, June 11-12. Dr. S. William Becker, 55 E. Washington St., Chicago 2, Secretary.

Society of Biological Psychiatry, Atlantic City, Chalfonte-Haddon Hall, June 12. Dr George N. Thompson, 1136 W. Sixth St., Los Angeles, Secretary.

Medical Legislation

STATE LEGISLATION

Alabama

Bills Introduced.—H. 46 proposes an appropriation of $3,000,000 annually to a **hospital and planning construction fund.** H. 124 proposes the creation of a state **medical education board** to provide loans and scholarships for students desiring to study medicine. H. 131 proposes to provide for **twenty-five scholarships** for the study of medicine at the University of Alabama Medical College, the persons selected to be chosen by the State Board of Health in consultation with the Dean of the University of Alabama Medical College. Recipients accepting a scholarship must agree to practice medicine for five years after the completion of medical training in an area of the state designated by the State Board of Health or else repay the amount of the scholarship immediately. H. 178 and S. 187 propose the creation of a **scholarship program** for advanced study in nursing to be administered by the state board of nurses' examiners and registration. S. 160 proposes to authorize the state board of health to provide an annual program throughout the state for the **early diagnosis of cancer.** Persons would be urged to report voluntarily to a duly licensed physician of their choice for an official examination, and anyone unable to pay the cost of such examination could register with the county health officer and arrange for a free examination. S. 198 proposes to provide for the examination of all children having **congenital or acquired malformations.** The county health officer would urge the parents of such children to arrange for an examination by a practicing pediatrician, orthopedist or physician of the parent's choice. If the parents are not able to pay for such examination the county health officer would make the examination or arrange to have it made at a "Well-Baby Clinic" or some other qualified clinic.

California

Bill Introduced.—S. 961 proposes the enactment of regulations for **the licensing of analytical toxicologists** and defines analytical toxicology **as** the analysis of any substance for the detection of poison.

Connecticut

Bill Introduced.—S. 1046 proposes to eliminate from the exemption section of the medical practice act persons practicing **massage or Swedish movement.**

Florida

Bills Introduced.—H. 189 proposes to bind the state by a regional compact looking toward the establishment and maintenance of jointly owned and operated **regional educational institutions** in the Southern states in the professional, technologic, scientific, literary and other fields so as to provide greater educational advantages and facilities for the citizens of the several states who reside within such regions. One of the institutions to be operated by this regional group would be the Meharry Medical College of Nashville, Tenn. H. 763 proposes the establishment of a **medical school** and college in Imperial Polk County, Fla. H. 775 proposes to authorize the state board of health to conduct research relating to the causes, prevalence and prevention of **diabetes,** to distribute information obtained therefrom for education of the public and to purchase at the lowest and best bid from a reliable manufacturer insulin of high quality for distribution for the treatment of indigent persons suffering from diabetes. H. 1087 proposes that no person, partnership, association or corporation shall establish, conduct or maintain **a chiropractic hospital,** sanatorium or related institution in the state without first obtaining a license from the State Chiropractic Board of Examiners. S. 550 proposes that the tuberculosis board shall provide adequate facilities for the compulsory isolation and treatment of persons found to be **suffering from tuberculosis.** S. 837, to amend the **law relating to dead bodies,** proposes that whoever buys, sells or has in his possession for the purpose of buying or selling or trafficking in the dead body of any human being shall be punished by imprisonment; provided, however, that nothing would prohibit the obtaining, dissecting, using and disposing of dead bodies for the purpose of teaching or other appropriate university research by any medical school, dental school, school of nursing or other university research or teaching unit which is a part of a regularly established or chartered institution of higher learning under the laws of the state of Florida.

Illinois

Bill Introduced.—H. 937 proposes regulations for the organization of health services plan corporations to furnish **voluntary health services.** A voluntary health services plan is defined as a plan or system under which medical, hospital, dental, nursing and related health services may be rendered to a subscriber or beneficiary at the expense of a health services plan corporation.

Oklahoma

Bill Introduced.—S. 301 proposes to authorize the state department of public health to create and maintain a **cancer control division** to promote a program for the prevention of cancer.

Texas

Bill Introduced.—H. 915 proposes to amend the 1949 **basic science law by** exempting therefrom graduates of schools of the healing arts who have been enrolled in their respective schools for at least one year prior to the time this act became law and who have attended the schools under the G. I. Bill of Rights and were bona fide residents of the state at the time they entered the military service, provided that this section shall not apply to any person who entered the military service after Jan. 1, 1946.

GOVERNMENT SERVICES

SECRETARY OF DEFENSE

UNIFICATION OF MEDICINE IN THE ARMED SERVICES

Acting to unify administration and operation of the medical services of the armed forces, Secretary of Defense Louis Johnson has established a medical services division within the Office of the Secretary of Defense.

The Secretary's directive provides for the appointment of a director of medical services for the National Military Establishment. He will have responsibility and authority to establish and control general policies, standards and programs for the medical services of the three military departments and related National Military Establishment agencies. In addition, Secretary Johnson set up an autonomous medical department for the Air Force, which heretofore has been served by personnel from the Army Medical Department. The new Air Force Medical Department will be headed by Major General Malcolm C. Grow, the Air Surgeon, who will retain that title.

The three military medical departments will retain their entity under Secretary Johnson's directive, but will operate under supervision by the National Military Establishment Medical Services Division similar to the strategic direction which the Joint Chiefs of Staff give to the unified commanders of the military departments.

The Director of Medical Services may be a civilian or an officer of one of the armed services. He will be appointed by the Secretary of Defense. His duties are defined as: (1) establishment and control of general policies, standards and programs for the medical services of the three military departments and appropriate agencies of the National Military Establishment; (2) to exercise general direction, authority and control over administration and utilization of personnel and facilities of the medical services of such departments and agencies through the heads thereof, and (3) such other duties with respect to the medical services of the National Military Establishment as the Secretary of Defense may direct.

In creating the National Military Establishment Medical Services Division and providing for an autonomous Air Force Medical Department, Secretary Johnson acted on the advice and recommendation of his Medical Advisory Committee, to which a recommendation of the Joint Chiefs of Staff that studies be made of measures intended to produce a unified National Military Establishment Medical Service was submitted. Charles Proctor Cooper, president of the Board of Trustees of Presbyterian Hospital in New York, is chairman of this committee, which is composed of eleven civilian physicians and dentists, the Surgeons General of the Army and Navy and the Air Surgeon.

With the establishment of the Air Force Medical Department, Secretary Johnson authorized the transfer to it for temporary duty of 100 Army and 100 Navy medical officers to help meet the shortage of medical personnel in the Air Force.

General hospitals serving Army and Air Force personnel will continue to be operated by the Army. Secretary Johnson also directed that general hospital training facilities of the Army and Navy be made available to the Air Force Medical Service on an equitable basis.

FIRST MEDICAL VOLUNTEERS CONGRATULATED

Secretary of Defense Louis Johnson on May 13 congratulated the first two young professional men who responded to the appeal for volunteers to overcome the shortage of physicians in the armed forces.

They are: First Lieut. James L. Patterson Jr., of Duncan, Okla., the first physician to volunteer for the Army, and Lieut. (jg) Milton M. Lownes Jr., of Philadelphia, the first physician to volunteer for the Navy.

The ceremony was held in the office of the Secretary of Defense in the Pentagon. The two young volunteers were introduced to Secretary Johnson by the heads of their respective medical departments, Major General Raymond W. Bliss, Surgeon General of the Army, and Rear Admiral Clifford A. Swanson, Surgeon General of the Navy.

ARMY

NATIONAL GUARD OFFERS COMMISSIONS TO MEDICAL GRADUATES

The 1949 medical school graduates who are not enrolled in R.O.T.C. medical units are being invited to accept commissions in the National Guard, Major General Kenneth F. Cramer, Chief, National Guard Bureau, announces.

Persons graduating from accredited medical schools this summer and beginning to serve their internships may be commissioned immediately as first lieutenants in the National Guard without previous military service.

"Under this program, young doctors and dentists are afforded an opportunity to identify themselves with National Guard outfits in more than 2,000 cities and towns throughout the forty-eight states, the District of Columbia, Hawaii and Puerto Rico," General Cramer stated.

Those who served in a commissioned capacity during World War II may receive commissions one grade higher than normally called for by the unit vacancy to which they would be assigned, provided they served in the higher grade during the war.

Doctors are particularly needed in time for service with the National Guard during the coming summer field training—most extensive in Guard history, with some 5,000 federally recognized Army and Air units participating.

R. O. T. C. SUMMER TRAINING

Medical students from professional institutions with one year or more of active military duty will participate in the summer training camp program at one of eight Army general hospitals instead of the previously planned training at the Medical Field Service School, Fort Sam Houston, Texas. This change is designed to place primary emphasis on military medicine, omitting a number of subjects of a purely military nature.

These revisions do not affect other medical R. O. T. C. students who are nonveterans. The nonveteran group will take part in the summer training program conducted at Fort Sam Houston.

Attendance at the general hospital camps is limited to students who have completed the sophomore year of their respective professional field in college. A qualified veteran, slated for Army general hospital training, may attend the field school at Fort Sam Houston if he so desires.

The period of the summer training program is June 13-September 9. This period is divided into two separate camps. The first will open June 13 and the second July 31; each lasting six weeks. The only exception to this Department of the Army ruling is for the first camp conducted at Letterman

General Hospital, San Francisco. There training will be given to medical students only, beginning May 31 and ending July 9.

During the summer at the Army general hospitals, these students will receive a minimum of orientation concerning military matters and, for the most part, will spend their time in the wards. They will attend as many of the regular formal teaching exercises as can be integrated into their program. Residents, interns and the attending staff assigned to the general hospital will furnish the bulk of the teaching. With few exceptions, the Army hospitals in which R. O. T. C. students will train are at present participating in medical training programs in nearby civilian institutions.

The eight Army general hospitals to be utilized this summer are as follows: Walter Reed, Washington, D. C.; Oliver, Augusta, Ga.; Percy Jones, Battle Creek, Mich.; Brooke, Fort Sam Houston; Fitzsimmons, Denver; Letterman, San Francisco; Madigan, Tacoma, Wash., and Valley Forge, Phoenixville, Pa.

ADVANCED TRAINING IN CIVILIAN INSTITUTIONS

The following Army Medical Department officers have been selected for advanced training in civilian institutions:

Joseph A. Connor Jr., Major	George Washington University School of Medicine, Washington, D. C.	Internal medicine
Thomas P. Jernigan III, Capt.	Baltimore City Hospitals	Medicine
Marvin D. Blackburn Jr., Capt.	St. Paul's Hospitals, Dallas 4, Texas	Pathology
John B. Sheffer, First Lieut.	Buffalo General Hospital	Pathology
John J. Carter, First Lieut.	University Hospital, Little Rock, Ark.	Obstetrics and gynecology
William P. Barron, First Lieut.	University Hospital, Little Rock, Ark.	Pediatrics
William W. Tucker, First Lieut.	Franklin Hospital, San Francisco	Medicine
Richard B. Johnson, First Lieut.	Indianapolis General Hospital	Intern training
Francis P. Martin, First Lieut.	Kings County Hospital, Brooklyn	Intern training

NAVY

NAVY LOANS 100 MEDICAL OFFICERS TO THE AIR FORCE

The Secretary of Defense on May 13, 1949, directed that thirty-five Naval medical officers be assigned temporarily to the U. S. Air Force for duty; sixty-five additional Navy medical officers are to report at a later date to be set by the Director of Medical Services of the National Military Establishment. The services of these doctors are urgently required by the Air Force until such time as doctors are procured to staff its own medical department.

This directive should not be construed as an indication that the Navy Medical Department is in excess, or has obtained its quota, of medical officers as the result of the current procurement program for doctors.

Regular and reserve medical officers now on active duty, and inactive reserve medical officers may volunteer for assignment to the Air Force. Those who request overseas duty will be permitted to take their families to the overseas Air Force facilities. These doctors will not be commissioned in the Air Force but will serve as Naval medical officers and wear the Navy uniform while so serving.

It is contemplated that, if those who volunteer have not already qualified as flight surgeons or aviation medical examiners, they will be ordered to Randolph Field, Texas, for a four week course of instruction in the technic of aviation examination and then assigned to Air Force facilities within the continental United States for duty, provided they have not previously indicated a preference for overseas duty. The maximum tour of duty with the Air Force has been set at two years.

Regular and active officers should submit applications to the Bureau of Naval Personnel via the Bureau of Medicine and Surgery. Inactive reserve officers should submit applications to the commandant of their local Naval District. Applications should be submitted prior to June 15, 1949.

REAR ADMIRAL ADAMS RETIRES

Rear Admiral John C. Adams, M.C., a pioneer naval flight surgeon, was transferred to the retired list on April 1 after more than thirty years of naval service. For outstanding services as flight surgeon in charge of the Division of Aviation Medicine, Bureau of Medicine and Surgery, during World War II, he was awarded the Legion of Merit. He received the John Jeffries Award from the Institute of Aeronautical Sciences for contributions to aviation in medical research for 1945.

NEW REGULAR OFFICERS

The following reserve medical officers have been appointed to the Medical Corps of the Regular Navy: Comdr. William S. Lawler, Lowell, Mass.; Comdr. Hermann J. Lukeman, New York, and Lieut. (jg) Victor G. Benson, Soldier's Grove, Wis.

FIRST ACTIVE DUTY AT NAVAL FACILITIES

The following lieutenants (jg) of the Medical Reserve Corps have been nominated for their first active duty at the Naval medical facilities indicated:

Name	Residence	Naval Facility
Adams, Barnette E. J., Jr.	New Orleans	Air Technical Training Center, Memphis, Tenn.
Austin, Robert R.	Dixon, Ill.	Naval Hospital, San Diego, Calif.
Kutschbach, Melvin A.	Houston, Texas	Naval Hospital, Corpus Christi, Texas
Settimi, Albino L.	Whittier, Calif	Naval Hospital, Corona, Calif.
Shershin, Peter H.	Clifton, N. J.	Naval Training Station, Newport, R. I.
Van Duyne, Charles M.	Pontiac, Ill.	Naval Dispensary, San Francisco

APPOINTMENT FOR POSTGRADUATE INSTRUCTION

The following medical officers have been nominated for postgraduate instruction: Comdr. Robert B. Johnson, York, Neb., to a residency in orthopedic surgery at the Naval Hospital, Oakland, Calif., and Lieut. (jg) Donald W. Grimes, Palmetto, Fla., to a residency in internal medicine at the Naval Hospital, Long Beach, Calif.

PERSONALS

Comdr. Ralph Volk, M.C., U.S.N.R., of Rutland Heights, Mass., has been nominated for recall to active duty and will be assigned to the Naval Hospital, St. Albans, N. Y., on completion of a course in internal medicine at Harvard Medical School, Boston.

Commander Peter G. Kroll of Mt. Carmel, Pa., and Lieutenant Francis H. McCullough Jr. of Jackson Heights, Long Island, N. Y., medical reserve officers, have requested recall to active duty and have been nominated to courses of instruction as residents in thoracic surgery and orthopedic surgery at the Naval Hospital, St. Albans, Long Island, N. Y., and the Naval Hospital, Philadelphia, respectively.

Commanders Chalmers R. Carr and Donald C. MacKinnon and Lieut. Comdr. William Charles Mulry have recently been certified by the American Boards of Surgery, Otolaryngology and Radiology, respectively.

Lieut. John H. Hege of Dover, Pa., and Lieut. (jg) Edward D. Loweecey of Pittsburgh have been nominated for their first active duty in the Regular Navy Medical Corps as residents, respectively, in internal medicine at the Naval Hospital, Bethesda, Md., and in internal medicine at the Naval Hospital in Philadelphia.

Lieut. Charles E. Weber of Rochester, N. Y., and Lieut. (jg) Roger K. Wallace of Ravenna, Neb., have been appointed to the Regular Navy Medical Corps from an active reserve status.

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Medical News

(Physicians will confer a favor by sending for this department items of news of general interest: such as relate to society activities, new hospitals, education and public health. Programs should be received at least two weeks before the date of meeting.)

CALIFORNIA

Book Plates of Physicians.—The Huntington Library at San Marino is developing a collection of book plates of physicians. Doctors who have book plates of their own or of others are invited to forward copies to the library to be entered in the collection.

New School of Tropical Medicine.—A School of Tropical and Preventive Medicine is to be developed in Loma Linda, in conjunction with the School of Medicine of the College of Medical Evangelists. Both graduate and undergraduate medical students will be given training in tropical medicine. Special short courses will be conducted for nonmedical missionaries preparatory to their departure for overseas posts. Dr. Harold N. Mozar, assistant professor of internal medicine of the school of medicine, has been named director of the new unit. During World War II Dr. Mozar served in New Guinea and was chief of the Communicable Diseases Section of the 47th General Hospital.

Medical Care Section Established.—A new Section in Medical Care Administration has been established by the School of Public Health at the University of California, Berkeley. This new curriculum complements the school's existing programs in hospital management and public health administration. Qualified graduate students may major in medical and hospital administration courses leading to the M.P.H. degree. Dr. Edward S. Rogers, dean of the school, heads the joint division. Dr. E. Richard Weinerman will be in charge of developing the new medical care curriculum. Drs. Sydney S. Norwick, Berkeley, and Dean A. Clark, New York, are part time visiting lecturers in the new section. A small research staff, headed by Charlotte F. Muller, Ph.D., is now engaged in medical economics field studies. The section will also be a repository of factual data in medical economics, and will serve as a source for consultation in problems of medical care, offering technical aid and other help to interested persons or organizations.

CONNECTICUT

Medical Service Plan.—Connecticut Medical Service enrolled 70,000 members in its first ten weeks of operation, representing 772 industrial and business firms. The plan was first offered to the public on February 14. Physicians participating in the plan numbered 1,272 as of May 15. This represents more than 85 per cent of the 1,479 physicians whose type of practice normally includes services covered by the plan. The number is increasing with the continued arrival of new agreements at the state medical society office. Robert S. Judd, president of the Connecticut Medical Service, has announced that the plan expects to pay surgical and maternity bills in volume from now on. The number of subscribers in the surgical plan now represents about 3½ per cent of Connecticut's population.

DISTRICT OF COLUMBIA

Hachmeister Memorial Lecture.—Hachmeister, Inc., of Pittsburgh, has established the A. C. Hachmeister Memorial Lectureship in the department of pharmacology of Georgetown University School of Medicine in memory of its founder and first president. Dr. C. Heymans, professor of pharmacology at the University of Ghent and Nobel Prize Laureate in medicine, 1938, delivered the first lecture May 4 on "The Role of Pressor and Chemo-Receptors in the Regulation of Respiration."

ILLINOIS

Commission for Handicapped Children.—Dr. Gerald M. Cline of Bloomington has been appointed a member of the Illinois Commission for Handicapped Children succeeding Dr. Bert I. Beverly, deceased. The commission is made up of the respective heads of the State Departments of Public Welfare, Public Health, Public Instruction and Labor, together with nine interested citizens appointed from the state at large by the Governor. The commission functions as a coordinating, fact-finding and stimulating agency charged with developing a more adequate statewide program for physically and mentally handicapped children. Dr. Cline is a native of Illinois, a veteran of World War I and a graduate of the University of Illinois College of Medicine, Chicago. He has been engaged in the practice of medicine since 1922, specializing in pediatrics and allergy. He is also on the advisory committee to the Division of Services for Crippled Children.

Chicago

Free Roentgen Examinations on Northwest Side.—A communitywide chest roentgenologic survey will be held during July and August on the near Northwest Side, which has one of the highest tuberculosis rates in Chicago. The Tuberculosis Institute and the Municipal Tuberculosis Sanitarium will conduct the survey using their two mobile x-ray units. Beginning July 5 free examinations will be made.

Award Willard Gibbs Medal.—The Chicago section of the American Chemical Society awarded its Willard Gibbs Medal May 20 to Peter J. W. Debye, Ph.D., of Cornell University, New York, in recognition of his work with high polymers, the giant molecules that make up rubber, plastics and proteins. Dr. Debye formerly was director of the Max Planck Institute in Berlin.

Home Care for Cancer Cases.—Michael Reese Hospital, under a grant from the Illinois Division of the American Cancer Society, will supply free home care for indigent cancer patients on an experimental basis. The program supplements one already in operation for heart patients. The service is being expanded to include patients with arthritis, diabetes and neurologic disease. Eight physicians from the hospital staff have been assigned to the four month cancer care program.

Acting Head of Division of Anesthesia.—Dr. Max S. Sadove, assistant professor of anesthesia at the University of Illinois College of Medicine, has been promoted to associate professor and acting head of the division of anesthesia. Dr. Sadove, a graduate of the University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, has been on the faculty for the past two years. Following his release from the army medical corps after five years' service, he served a residency in anesthesia at the Veterans Administration Hospital, Hines. He will continue to serve as consultant in anesthesia at Hines and at the City of Chicago Municipal Tuberculosis Sanitarium.

KANSAS

Society News.—The Kansas Psychiatric Society elected the following officers for the year ending April 1950: Dr. Clarence J. Kurth, Wichita, president, and Dr. Frank F. Merker, Topeka, secretary-treasurer.

Community Honors Fifty-Year Practitioner.—A citywide celebration for Dr. James A. McLaughlin, Wichita, was held by the citizens of Greensburg, where he has spent the greater part of fifty years of practice. An open house and tea were held in the community building, and a dinner for all friends and relatives took place at the Baptist Church.

KENTUCKY

Annual Health Conference.—The first annual conference on health in Kentucky will be held June 23 at Warren Memorial Presbyterian Church, Louisville. The all day session will present a statewide view of health problems including those pertaining especially to tuberculosis, mental illness, rural health, medical care and school health.

Appoint Director of Blood Center.—Dr. Alberta B. W. Baugh, Louisville, has been appointed technical director of the Red Cross Regional Blood Center, which was opened by the Mayor of Louisville May 18. The center will collect and supply blood in an area within a 75 mile radius of Louisville. Dr. Baugh is a graduate of the University of Louisville School of Medicine, 1939.

MAINE

Dr. Ames Resigns Hospital Post.—Dr. Forrest B. Ames, Bangor, president of the Maine Medical Association, resigned April 1 as head of the department of roentgenology at Eastern Maine General Hospital after twenty-six years of service. He is opening a private practice in Bangor.

Anniversary Reunion at Jackson Laboratory.—An open invitation has been issued to attend the Roscoe B. Jackson Laboratory's Twentieth Anniversary Reunion of visiting investigators and summer students at Bar Harbor August 18-21. The reunion will be part of the four-day observances, during which dedication ceremonies for the rebuilt laboratory will take place. Because of the destruction of some of the records during the fire of October 1947, the laboratory does not have a complete list of former associates and students. If any one of these

wishes to attend any part or all of the anniversary reunion, he should get in touch with the laboratory at once as there is still a shortage of housing accommodations in Bar Harbor, and full details will be sent.

MASSACHUSETTS

Dr. Cohn Named University Professor.—Edwin J. Cohn, Ph.D., professor of biological chemistry and chairman of the Division of Medical Sciences, Harvard Medical School, Boston, has been appointed a university professor. He is one of four scholars especially chosen for work on the frontiers of knowledge and will be free of obligation to any individual school or department within the university. He will continue his research in physical biochemistry. Dr. Cohn's appointment follows the retirement of Prof. Roscoe Pound, who was the first scholar to hold a university professorship. Dr. Cohn has served in the department of physical chemistry at the medical school since 1922, and has been professor of biological chemistry and head of the department since 1935. He is a graduate of the University of Chicago, 1917, and a recipient of the John Phillips Memorial Medal of the American College of Physicians, 1946, the Passano Award, 1945, and the Alvarenga Prize of the College of Physicians of Philadelphia, 1942. He serves at present on the Panel on Hematology of the U. S. Public Health Service and on the Committees on Blood and Blood Derivatives of the American Red Cross and the National Research Council. He has been an honorary consultant to the Medical Department of the Navy since 1942.

NEW HAMPSHIRE

State Medical Meeting.—The annual meeting of the New Hampshire Medical Society will be held at the Hotel Wentworth, New Castle, June 14-15 under the presidency of Dr. Clarence E. Dunbar, Manchester. Out of state speakers include:

John R. Paul, New Haven, Conn., Clinical Considerations of Acute Poliomyelitis.
J. William Hinton, New York, Significance of Abdominal Pain.
David S. Grice, Boston, Orthopedic Problems and Their Management in the Newborn.
Wallace E. Herrell, Rochester, Minn., Present Status of Antibiotic Therapy.
Frank H. Lahey, Boston, Surgical Management of Lesions of the Terminal Ileum, Colon and Rectum.
Basil C. MacLean, Rochester, N. Y., The Hoopskirts of Hospital Finance.

On Tuesday morning there will be a symposium on the Economic Phases of Hospital Administration with James M. Langley, Concord, president of the Blue Cross in New Hampshire, as moderator. Round table conferences in seven specialties are scheduled for Wednesday morning. At the annual banquet Tuesday at 7 p. m. Sherman Adams, governor of New Hampshire, and Dr. George F. Lull, Secretary, American Medical Association, Chicago, will be the speakers.

NEW YORK

Research on Hemorrhagic Shock.—A grant of $29,370 has been made to the University of Buffalo by the Veterans Administration for research on red blood cells in relation to hemorrhagic shock. The one year grant was made through the National Research Council, and is renewable as the project continues. The research will be headed by Dr. John D. Stewart, professor of surgery and chairman of the department of surgery in the medical school. There will be three major investigators: Dr. L. Edgar Hummel, a hematologist; Joseph G. Hoffman, Ph.D., a biophysicist, and Dr. Irving Rudman, Buffalo, a surgical assistant, besides three technicians. The project, known as "Physiological Adjustment to Hemorrhage and the Fate of the Transfused Red Blood Cell," will involve the use of radioisotopes, which will be obtained through the Atomic Energy Commission.

New York City

Dr. Selye to Address Alumni.—New York Medical College, Flower and Fifth Avenue Hospitals Alumni Day will be held June 7. Included in the activities will be the second annual Alumni Lecture by Dr. Hans Selye, professor of experimental medicine and surgery, University of Montreal Faculty of Medicine, at 11 a. m. on "Hypertension as a Disease of Adaptation." The annual banquet will be held at 6:30 in the Grand Ball Room, Ritz-Carlton Hotel.

Report on Examinations for Tuberculosis.—The New York Tuberculosis and Health Association reports that 9,119 chest roentgenograms were taken by the Bronx Tuberculosis and Health Committee last year, and 2,783 families and individuals were aided in their health programs. More than 50,000 persons attended meetings, lectures, motion pictures and exhibits held under committee auspices. During the year 3,842 parochial school pupils had received audiometer tests, and 54 hearing defects requiring attention had been discovered. Dr. Nathan B. Van Etten was reelected chairman of the committee.

OHIO

Personals.—Dr. Morris Schaeffer, assistant professor of pediatrics at Western Reserve University School of Medicine, Cleveland, and director of the contagious department of the Cleveland City Hospital, has resigned from these posts, effective June 30, and will leave Cleveland to assume new responsibilities as director of the Virus and Rickettsial Research and Epidemiology Branch of the Communicable Disease Center of the U. S. Public Health Service.——Dr. John A. Toomey has returned from his sabbatical leave in Florida to resume his duties as head of the contagious department.——Dr. Calvin L. Baker, superintendent of Dayton State Hospital, has been appointed commissioner of mental hygiene for Ohio.

Short Courses in Poliomyelitis.—At the department of contagious diseases, City Hospital, Cleveland, Dr. John A. Toomey will direct a series of short training courses in poliomyelitis. The dates of the courses for physicians are July 18-23, August 8-13 and August 29-September 3. The National Foundation for Infantile Paralysis will pay the expenses of the enrollee, providing the chairman of his local chapter approves. Meals may be purchased at the hospital, but each enrollee is responsible for his own hotel reservations. There will also be courses for nurses and physical therapists. For complete programs write to Dr. Toomey, City Hospital, Cleveland.

PENNSYLVANIA

Society News.—The Pennsylvania Academy of Ophthalmology and Otolaryngology at its annual meeting April 22-24 in Harrisburg installed Dr. Daniel S. DeStio, Pittsburgh, president and chose Drs. Jay G. Linn, Pittsburgh, president elect, Benjamin F. Souders, Reading, secretary, and Bruce A. Grove, York, treasurer.

Philadelphia

Ex-Interne-Resident Dinner.—The annual dinner of the Ex-Interne-Resident Association of the Hospital of the University of Pennsylvania will be held at the Hotel Sylvania, Philadelphia, June 10 at 6:30 p. m. Subscription will be $5. Reservations may be secured from John W. Frost, M.D., Hospital of the University of Pennsylvania.

Temple University News.—Recent staff appointments at Temple University Medical School and Hospital include Drs. George D. Vaughan Jr., Philadelphia, instructor in proctology; George W. Russell, Philadelphia, assistant instructor in psychiatry, and Sydney A. Ellis, Boston, associate professor of pharmacology. Recent gifts totaling $1,388 have been made to the Psychiatric Department Research Fund, and $5,100 has been received for research in ophthalmology.

New Course in Anesthesiology.—A comprehensive eight month course in anesthesiology will be offered in the Graduate School of Medicine of the University of Pennsylvania beginning in October. The chairman of the newly created department is Dr. Robert D. Dripps, professor of anesthesiology, Graduate School of Medicine, and director of anesthesiology at the Hospital of the University of Pennsylvania. The program will provide training in basic as well as clinical sciences. The university's announcement said that new approaches in pedagogy will characterize the course. Panel discussions and presentations of clinical cases will supplement formal lectures. This section is to be headed by Drs. Julius H. Comroe Jr., Seymour S. Kety, David L. Drabkin and William E. Ehrich. In an attempt to assure a broad clinical foundation for the anesthesiologist, it was explained, training in cardiology, neurology and radiology will be provided. Clinical preceptorships will be served in eight to ten Philadelphia hospitals in which there are departments of anesthesia staffed by physicians. The course is not intended to compete with or replace a required and supervised residency in anesthesiology in an accredited hospital. Designed after careful thought and with the advice of the American Board of Anesthesiology, it is offered as a supplement, or precursor, to such resident training.

Pittsburgh

$300,000 Gift for Medical Library.—The University of Pittsburgh has received a gift of $300,000 from the Maurice and Laura Falk Foundation to construct a medical library in the proposed new school of medicine. The library will be known as the Maurice and Laura Falk Library, and its initial collection will include more than 50,000 volumes. It is to be located on the first floor of the new school and will be officially the library of the Allegheny County Medical Society.

SOUTH CAROLINA

Personal.—Dr. Harry F. Wilson, Columbia, has been elected director of the Division of Laboratories of the South Carolina State Board of Health. He has been serving as acting director of laboratories since July 1947, as well as director of the Division of Industrial Health.

State Medical Association Meeting.—The annual meeting of the South Carolina Medical Association was held at the Ocean Forest Hotel, Myrtle Beach, May 17-19 under the presidency of Dr. Robert B. Durham, Columbia. Guest speakers included:

Edward B. Sheehan, Boston, Carcinoma of the Endometrium.
Frank P. Coleman, Richmond, Va., Treatment of Fractured Ribs.
H. Hudnall Ware Jr., Richmond, Va., Management of Some Usual Obstetrical Difficulties.

WASHINGTON

Breakfast Study Club in Tacoma.—The Tacoma chapter of the American Academy of General Practice has organized a breakfast study club, which will meet on Friday mornings to consider ways and means of making the family doctor available to all people of Tacoma and to keep him abreast of the latest developments in medical science. All physicians are invited to participate in the discussions.

Allen Lecture.—The second annual Raymond B. Allen Lectureship, honoring the president of the University of Washington, was held May 27. The lectureship consisted of a symposium on The Medical Aspects of Nuclear Energy with the following participants: Dr. Joseph G. Hamilton, associate professor of experimental medicine and radiology, University of California, Berkeley, and Dr. Simeon T. Cantril, associate clinical professor of radiology, University of Washington School of Medicine, director of the Tumor Institute, Swedish Hospital, Seattle. This lectureship is sponsored by the local chapter of the Phi Beta Pi Medical Fraternity.

WEST VIRGINIA

Society News.—Dr. Garnett P. Morison, Charles Town, was elected president of the West Virginia Academy of Opthalmology and Otolaryngology at the annual spring meeting held at Martinsburg May 13-14. Dr. Melvin W. McGehee of Huntington and Dr. Frederick C. Reel of Charleston were reelected secretary and treasurer, respectively.

Temporary Licensing of Interns and Residents.—At a meeting of the public health council at Charleston May 12 regulations were promulgated for the temporary licensing of interns and residents. The regulations were adopted to provide means to alleviate to some extent the critical doctor shortage in rural areas, especially coal mining communities. Participating interns and residents must be graduates of class A medical schools and must be serving in hospitals fully accredited by the American Medical Association or the American College of Surgeons. Applicants and sponsors will be given letters of authorization by the secretary of the medical licensing board, and legal responsibility will be assumed by the sponsor, who will be required to report to the licensing board and the hospital whether or not the services of the relief physician are satisfactory. The time spent on relief work by a doctor shall not exceed thirty days each twelve months of hospital service, and the sponsor will be required to spend a reasonable length of time with the relief doctor for indoctrination. The participating physician will take care of all regular reports, filing of birth and death certificates and communicable disease reports. The relief doctor's signature will be valid on all state documents, insurance papers and compensation reports during the relief period.

WISCONSIN

Veterans Hospital Clinical Day.—Woods Veterans Hospital will hold a Clinical Day program June 30 at the hospital to which all physicians are invited. Drs. Michael F. Koszalka and Albin J. Krygier will be chairmen of the morning and afternoon sessions respectively.

Personal.—Dr. James C. Sargent, clinical professor of urology at Marquette University, Milwaukee, and a captain in the Naval Medical Corps Reserve, has been appointed a member of the Board of Reserve Consultants to the Surgeon General of the Navy.

Research on Arthritis and Rheumatism.—An intensive study of arthritis and rheumatism will be initiated at the University of Wisconsin following a gift of $10,300 from the Thomas E. Brittingham Trust Fund. Dr. Daniel M. Angevine and Dr. Charles H. Altshuler of the department of pathology, who have been conducting histochemical studies of rheumatic disease for two years, will receive $5,300 to finance their work. Four thousand dollars will be used for electromyographic apparatus for the study of muscular changes in arthritic conditions. Dr. Charles V. Seastone of the department of microbiology will use $1,000 of the gift to investigate sensitization reactions to streptococci in rheumatic and arthritic states.

ALASKA

Anchorage Medical Society.—This society, which was recently organized through the efforts of Colonel Stanley W. Matthews, M.C., U. S. Army, will hold meetings each month, alternating between Anchorage and the 183rd Army General Hospital. The society is open to all physicians, civilian or military, in good standing who live in the vicinity of Anchorage. Officers elected for the current year are: Colonel Matthews, president; Dr. George G. Davis, Anchorage, vice president; Dr. Milo H. Fritz, Anchorage, secretary, and Major Robert B. Franklin, M.C., U. S. Army, treasurer.

PUERTO RICO

Legislation for School of Tropical Medicine.—The Insular Legislature has approved a bill to authorize the Superior Board of Education of the University of Puerto Rico to establish a school of medicine, giving the board also jurisdiction over the administration of the School of Tropical Medicine, San Juan, now operating under the guidance of Columbia University, New York. The School of Tropical Medicine is now under the direction of a board of trustees, five of whom are members of the Superior Board of Education of the University of Puerto Rico, and two of Columbia University. The director and the members of the faculty of this school serve at the will of the board of trustees of Columbia University. The bill, now pending approval of the governor, will change the administration, giving jurisdiction to the University of Puerto Rico.

GENERAL

Phi Chi Luncheon.—Phi Chi medical fraternity will hold a luncheon June 9 at 12:45 p.m. at the Ambassador Hotel in Atlantic City, N. J. Tickets will be available at the Phi Chi registration desk in the fraternity and alumni registration area at Convention Hall.

Railroad Surgeons Meeting.—The annual meeting of the American Association of Railway Surgeons will be held at the Drake Hotel, Chicago, June 30 to July 2, under the presidency of Dr. Raymond B. Kepner, Chicago. A symposium on Intrathoracic Disorders is scheduled for Thursday afternoon and another on Bone and Joint Lesions for Friday afternoon.

Proctology Meeting.—The newly organized International Academy of Proctology will hold its first meeting at the Marlborough-Blenheim in Atlantic City, N. J., June 10. The scientific program will include motion picture films of rectal surgery. Papers on proctologic subjects will be presented by Drs. Earl J. Halligan, Jersey City, N. J.; Edgar M. Scott, Birmingham, Ala.; Caesar Portes, Chicago, and William Lieberman, Brooklyn.

Pamphlets on Cancer Sites.—The American Cancer Society in cooperation with the National Cancer Institute, Bethesda, Md., has prepared four cancer pamphlets. The sites considered are: (1) the breast, and (2) female generative organs, where nearly 40 per cent of cancers fatal to women start; (3) the digestive organs, which account for nearly 50 per cent of all cancer deaths, and (4) the mouth and respiratory tract, including the lungs and bronchus, where reported cancer mortality in men has increased over 300 per cent in the last fifteen years. The pamphlets can be obtained without charge through most of the local or state offices of the society's sixty-one divisions or the national office at 47 Beaver Street, New York City.

Dr. Burnell Succeeds Dr. Selby at General Motors.—Dr. Max R. Burnell, Flint, Mich., will become medical consultant to General Motors Corporation effective July 1, succeeding Dr. Clarence D. Selby, who is retiring after fourteen years of service. Dr. Burnell, a graduate of the University of Michigan Medical School, Ann Arbor, 1918, has been medical director of the AC Spark Plug Division of General Motors since 1931, when he organized it as one of the first certified industrial medical departments in America. Its modern equipment and advanced technics have long been recognized as outstanding in medical circles throughout the country. For many years Dr. Selby has served as a special lecturer at the School of Public Health of the University of Michigan, where, after his retire-

ment, he will assist in the development of a program in the field of industrial health. Last year Dr. Selby inaugurated a cooperative program between the company and medical schools whereby graduates from these schools are able to take their internship in General Motors plants (THE JOURNAL, March 26, p. 864).

Committee on Habit-Forming Drugs.—The World Health Organization has selected Dr. Nathan B. Eddy as chairman of its Expert Committee on Habit-Forming Drugs. Dr. Eddy has been a leader in investigating the use of narcotics in the control of pain in cancer. In 1939 he shared with Dr. Lyndon F. Small of the National Institutes of Health the first annual award of the American Pharmaceutical Manufacturers Association for discovery of the drug metopon. Among his university appointments is that of research professor in pharmacology at the University of Michigan from 1930 to 1939. Dr. Eddy is also secretary of the Committee on Drug Addiction and Narcotics of the National Research Council.

American Society for the Study of Sterility. — This society will hold its annual conference at the Hotel Strand, Atlantic City, N. J., June 6-7 under the presidency of Dr. Lyman W. Mason, Denver. Those presenting papers by invitation include:

Samuel R. M. Reynolds, Ph.D., Brooklyn, Problems in Uterine Physiology and Their Interpretations.
Samuel R. Meaker, Boston, Ovarian Resection for the Relief of Sterility.
Marvin R. Thompson, Ph.D., New York, Nutritional Requirements in Human Reproduction.
James L. Royals, Pittsburgh; Carlton N. Price, Washington, and Paul Titus, Pittsburgh, Hysterosalpingography—Dangers and Their Prevention.
William H. Perloff, Philadelphia, Extraction of Human Hyaluronidase from Human Testes and Semen.

The speaker at the annual dinner Monday at 7 p. m. will be William W. Greulich, Ph.D., of the National Research Council, whose subject will be "Hiroshima and Nagasaki, 1947 and 1948."

Publication on School Health Policies.—Contributing toward the improvement of health programs for school children, which is one phase of the general theme of the 1949 Child Health Day May 1, more than 105,000 copies of "Suggested School Health Policies"—a charter for school health—have been distributed by the Health Education Council. "Suggested School Health Policies" not only has contributed to building a healthier America for American children, but has also contributed to the rehabilitation of the Japanese school system. American Military Government teams have ordered this 48 page guide for use in developing up-to-date school health policies in Japan. The booklet was prepared by a committee representing fifteen national organizations concerned with health and education. It may be obtained from the Order Department, American Medical Association, 535 N. Dearborn Street, Chicago, Ill. The price of the booklet is 25 cents; single copies are free to persons engaged in health education. The booklet can also be ordered in quantity from Health Education Council, 10 Downing St., New York 14.

National Vitamin Foundation.—Dr. E. Gifford Upjohn, vice president, the Upjohn Company, Kalamazoo, Mich., was elected president of the National Vitamin Foundation for 1949 at the annual meeting of foundation members in New York. Dr. Upjohn succeeds Basil O'Connor, New York, president of the American Red Cross, who was named to the newly created position of honorary chairman of the Board of Governors. J. Paul Folsom, Lederle Laboratories Division, American Cyanamid Company, New York, was elected board chairman. Dr. Robert S. Goodhart, scientific director, in his annual report revealed that by the end of 1948, the foundation's third year, a total of $186,633.72 has been appropriated for grants-in-aid for research and educational activities. A total of 30 grants-in-aid have been made to 17 institutions for the support of 23 research projects. During 1948, 7 grants-in-aid were continued and 7 new research projects instituted, according to the report. Among educational activities assisted with grants from the foundation during 1948 were publication of the "Handbook on Clinical Nutrition" of the Food and Nutrition Board of the National Research Council, toward which $12,000 was contributed, and a grant to Washington University School of Medicine, St. Louis, of $1,225.42 to defray costs of its Nutrition Symposium. As part of its educational activities, the foundation also spent $10,312.17 to arrange about 4,500 bookings of the foundation's motion picture "Strange Hunger." The foundation's board of governors was increased to eighteen members. Newly elected members were Mr. W. R. McHargue, E. R. Squibb & Sons, New York, and Dr. Ernest H. Volwiler, Abbott Laboratories, North Chicago, Ill.

FOREIGN

Postgraduate Courses in Vienna.—Postgraduate courses for physicians and surgeons are now being offered at the University of Vienna in Austria, which, for the first time since the war, is opening its postgraduate school for doctors from overseas and is able to provide suitable living accommodations.

Anderson-Berry Medal Award.—A David Anderson-Berry silver-gilt medal, together with a sum of money amounting to about 100 pounds, will be awarded in 1950 by the Royal Society of Edinburgh to the person, who, in the opinion of the Council, has recently produced the best work on the therapeutical effect of roentgen rays on human diseases. Applications for this prize are invited. They may be based on both published and unpublished work and should be accompanied by copies of relevant papers. Applications must be in the hands of the general secretary, Royal Society of Edinburgh, 22 George Street, Edinburgh 2, by March 31, 1950.

Australian Postgraduate Federation.—A federation to be known as the Australian Postgraduate Federation in Medicine has been formed with the object of encouragement and advancement of postgraduate medical education, work and research in Australia. In addition the federation will deal with matters common to more than one postgraduate committee, and particularly with the arrangements for visits of teachers to Australia. The formation of the federation will in no way limit the committee in the exercise of its own independent functions in its own state. The members of the federation are the Melbourne Permanent Post Graduate Committee, the Post-Graduate Committee in Medicine in the University of Sydney, the Post Graduate Committee in Medicine of the University of Adelaide, the Postgraduate Medical Education Committee of the University of Queensland, the Western Australian Post Graduate Committee (British Medical Association) and the Tasmanian Post-Graduate Committee in Medicine. Provision has been made to admit to membership organizations from New Zealand or elsewhere on certain conditions. A president, vice president and an executive committee will be appointed each year and the executive committee will be elected from persons nominated by the postgraduate committee of the state chosen for this purpose by the federation.

Israeli Medical School Opens.—The Hebrew University–Hadassah Medical School, the first medical school to be established in Israel, opened its doors May 17 as a joint undertaking of the Hebrew University and Hadassah, the women's Zionist organization of America. Until security conditions permit continuation of construction on Mt. Scopus, the site of the present 400 bed Rothchild-Hadassah-University Hospital, the school will be housed in four hospital units totaling initially over 300 beds in the city of Jerusalem proper. A class of 50 has been admitted, and a like number will be admitted in April 1950. By 1951 the first regular class will be admitted to the full six year course of instruction, the first two years of which will cover the premedical studies and the last four years the standard American medical course. Nearly $4,000,000 of the necessary $5,500,000 needed to complete school building program has been raised.

One of the first visiting professors is Dr. Samuel Standard, New York University College of Medicine–Bellevue Medical Center, who will inaugurate instruction in surgery at the school. Among members of the faculty are Bernhard Zondek, gynecology; A. Feigenbaum, ophthalmology; S. E. Franco, pathologic anatomy; Saul Adler, parasitology, and L. Olitzki, bacteriology.

Marriages

JAMES A. VAUGHN JR., West Palm Beach, Fla., to Dr. Phyllis A. Petersen of Baltimore, in March.

JOHN ROBERT SHELL, Lawrenceville, Va., to Miss Betty Jane Moseley of Lake Charles, La., April 23.

ERNEST RANDOLPH TRICE to Miss Virginia Dorsey Brown, both of Richmond, Va., May 7.

LEE R. SANBORN to Mrs. Hildegard Tropp Wolf, both of Angola, N. Y., February 14.

WILLIAM BERNARD YEGGE to Miss Marion Agnes Fleisch, both of Denver, January 19.

EDWARD C. RAFFENSPERGER to Dr. Mary Ames both of Harrisburg, Pa., April 9.

JOHN J. LITZ, New York, to Miss Carolyn Weir of San Francisco, in April.

Deaths

Charles Wesley Adams, Franklin, N. H.; Boston University School of Medicine, 1884; member of the American Medical Association; on the staff of the Franklin (N. H.) Hospital and Memorial Hospital in Concord; formerly mayor; bank president; died March 12, aged 85, of heart failure.

Thomas John Barb ✠ Roby, Texas; University of Oklahoma School of Medicine, Oklahoma City, 1921; on the staff of the Fisher County Memorial Hospital, where he died February 24, aged 61, of pneumonia.

Karl Mikael Beck ✠ Waukegan, Ill.; Loyola University School of Medicine, Chicago, 1918; formerly county physician and superintendent of Lake County General Hospital; died March 19, aged 55.

Nathan Berger ✠ New York; Long Island College Hospital, Brooklyn, 1917; on the staff of the New York Eye and Ear Infirmary; died February 12, aged 56, of carcinoma of the stomach.

Kenneth Edwin Blair ✠ Detroit; Northwestern University Medical School, Chicago, 1938; on the staffs of Grace and Holy Cross hospitals; died February 28, aged 38.

John Blake, Detroit; Detroit College of Medicine, 1907; died March 15, aged 66, of carcinoma of the colon.

William Floyd Boze, Carthage, Tenn.; University of Tennessee Medical Department, Nashville, 1892; for many years county health officer; died March 11, aged 79.

Joseph Bernard Brain ✠ Isabella, Pa.; University of Pittsburgh School of Medicine, 1927; served overseas during World War II; died in the U. S. Veterans Administration Hospital, Aspinwall, March 19, aged 45, of coronary thrombosis.

William Norwood Breckinridge, Fincastle, Va.; University of the South Medical Department, Sewanee, Tenn., 1904; member of the American Medical Association; served during the Spanish-American War and World War I; for many years county coroner and mayor of Fincastle; died March 21, aged 73, of angina pectoris.

Wallace McMurray Burroughs, St. Charles, Ill.; Northwestern University Medical School, Chicago, 1893; member of the American Medical Association; died March 25, aged 78, of chronic myocardial degeneration.

Lewis Angus Wood Burtch ✠ Phoenix, Ariz.; Rush Medical College, Chicago, 1897; member of the American Society of Anesthetists; died recently, aged 73.

J. Willard Caldwell, Steamboat Rock, Iowa; St. Louis College of Physicians and Surgeons, 1901; served during World War I; died March 24, aged 68.

Harry Edward Castle, San Francisco; Rush Medical College, Chicago, 1905; died March 29, aged 74, of hypertensive cardiovascular disease.

Burt Thomas Church ✠ North Hollywood, Calif.; University of Nebraska College of Medicine, Omaha, 1923; died March 12, aged 50.

George Henry Cottral ✠ Savanna, Ill.; Marion-Sims-Beaumont Medical College, 1903; served during World War I; died in the Kahler Hospital, Rochester, Minn., March 16, aged 73, of carcinoma of colon.

Samuel Wright Crittenden, Wakefield, Mass.; Dartmouth Medical School, Hanover, N. H., 1898; Medical School of Maine, Portland, 1898; member of the American Medical Association; formerly medical officer in charge of the U. S. Veterans Hospital and on the staff of State Hospital in Boston; died March 26, aged 91, of cerebral hemorrhage and arteriosclerosis.

Stanton Curry ✠ Peekskill, N. Y.; New York University, University and Bellevue Hospital Medical College, 1898; an Associate Fellow of the American Medical Association; on the staff of Peekskill Hospital; bank president; died March 26, aged 79, of lymphatic leukemia.

James Bayard Gregg Custis ✠ Washington, D. C.; New York Homeopathic Medical College and Hospital, New York, 1907; served during World War I; on the staff of the National Homeopathic Hosptial; for many years affiliated with Florence Crittenton Home; died February 28, aged 66, of coronary occlusion.

Fred Beam Cyphers, Duncan, Neb.; Lincoln (Neb.) Medical College, 1905; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1907; member of the American Medical Association; affiliated with St. Mary's and Lutheran hospitals in Columbus; died in the Mayo Clinic, Rochester, Minn., March 22, aged 65, of carcinoma.

Robert Anthony Davis, Ludington, Mich.; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1906; served on the staffs of the Woman's and Providence hospitals in Detroit and the Paulina Stearns Hospital; died March 29, aged 84.

William Earl Dawson, Hookerton, N. C.; Jefferson Medical College of Philadelphia, 1920; member of the American Medical Association; died recently in Raleigh, aged 54, of coronary thrombosis.

George Valentine Dorsheimer ✠ Dewey, Okla.; University Medical College of Kansas City, Mo., 1913; on the staff of the Memorial Hospital, Bartlesville, where he died March 16, aged 73, of carcinoma.

Robert Lee Dossett, Tullahoma, Tenn.; University of Tennessee Medical Department, Nashville, 1908; mayor; served as state senator; for many years city health officer; member of the Coffee County Court; died in the Gartly-Ramsay Hospital, Memphis, March 27, aged 68, of pneumonia, following a broken hip received in a fall.

John Frederick A. Drew, Portland, Ore.; Northwestern University Medical School, Chicago, 1896; died March 13, aged 82, of cerebral hemorrhage.

Thomas Nelson Duncan, Onaway, Mich.; St. Louis University School of Medicine, 1903; died in Cheboygan March 6, aged 71.

Roland Jordan Dunn ✠ Chicago; Rush Medical College, Chicago, 1897; on the staffs of St. Anne's and Bethany hospitals; died March 10, aged 73, of cerebral thrombosis.

Elling H. Ellingsen, Calmar, Iowa; Bennett College of Eclectic Medicine and Surgery, Chicago, 1898; died March 12, aged 87, of hypostatic pneumonia and arteriosclerotic heart disease.

Samuel Henry Freeman, Nashville, Tenn.; Meharry Medical College, Nashville, 1928; professor of anatomy and surgery (orthopedic) at his alma mater; chief physician and head of the health department of Tennessee A. & I. State College; affiliated with Hubbard Hospital; died March 24, aged 50, of coronary heart disease.

Rolland Edward Gardner, Reynoldsburg, Ohio; University of Louisville (Ky.) School of Medicine, 1929; member of the American Medical Association; died March 24, aged 47, of coronary thrombosis.

Edgar James Gilray, Cuba, N. Y.; University of Buffalo School of Medicine, 1891; member of the American Medical Association; formerly medical superintendent of Erie County Hospital in Buffalo; died in Cuba Memorial Hospital March 27, aged 82, of arteriosclerosis.

George Spaulding Greene, Dowagiac, Mich.; Detroit College of Medicine, 1897; member of the American Medical Association; served during World War I; formerly practiced in Gary, Ind., where he was on the staff of Mercy Hospital; died in Pawating Hospital, Niles, March 22, aged 73, of cerebral hemorrhage.

James Anthony Guilfoil ✠ San Francisco; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1911; served during World War I; affiliated with St. Francis Hospital and Southern Pacific Hospital, where he died March 7, aged 61, of coronary occlusion and arteriosclerotic hypertensive heart disease

Joseph A. Haluska ✠ Detroit; Magyar Királyi Pázmány Petrus Tudomanyegyetem Orvosi Fakultasa, Budapest, Hungary, 1923; served on the city planning commission; on the staff of St. Joseph's Hospital, where he died March 12, aged 49, of pulmonary emboli and portal cirrhosis.

Benjamin Charles Hamilton Sr., Jefferson, Iowa; College of Physicians and Surgeons, Keokuk, 1882; member of the American Medical Association; died March 20, aged 89.

Charles Carter Hamilton ✠ Philadelphia; State University of Iowa College of Medicine, Iowa City, 1923; specialist certified by the American Board of Radiology; member of the New England Roentgen Ray Society; on the staff of Chestnut Hill Hospital; died in the University of Pennsylvania Hospital March 28, aged 51, of bronchopneumonia.

Bell DeVan Hansell ✠ Okolona, Miss.; College of Physicians and Surgeons, Memphis, Tenn., 1911; formerly medical director and owner of a hospital bearing his name; died March 7, aged 61.

Charles Herbert Haskins, Saranac Lake, N. Y.; Yale University School of Medicine, New Haven, 1923; served during World War I; accidentally drowned recently, aged 53.

Bernard N. Hatcher, Baltimore; University of West Tennessee College of Medicine and Surgery, Memphis, 1914; died in Provident Hospital recently, aged 58, of hypertensive cardiovascular renal disease.

Robert J. Heavenridge, Hannibal, Mo.; Central Medical College, St. Joseph, Mo., 1897; died in March, aged 76.

Jeannette Potter Himmelsbach, Buffalo; University of Buffalo School of Medicine, 1890; died March 12, aged 81, of cerebral thrombosis.

Joseph Howerton Hopper, Willisburg, Ky.; Hospital College of Medicine, Louisville, 1898; member of the American Medical Association; died February 3, aged 72, of organic heart disease.

Harold Lee Hurley ⊕ Jackson, Mich.; Detroit College of Medicine, 1913; past president of the Jackson County Medical Society; fellow of the American College of Surgeons; served during World War I; on the staffs of the W. A. Foote Memorial and Mercy hospitals; died March 11, aged 58, of cardiac failure.

Dennis Bliss Jarrell, Beckley, W. Va.; College of Physicians and Surgeons, Baltimore, 1915; member of the American Medical Association; served overseas during World War I; on the staff of Raleigh General Hospital; died March 30, aged 62, of primary spinal atrophy.

Francis H. Jenkins, Italy, Texas; Chattanooga (Tenn.) Medical College, 1902; died in Columbus, Ohio, March 9, aged 75.

Arthur Henry N. Juengel, St. Louis; St. Louis University School of Medicine, 1908; died March 8, aged 66, of heart disease.

Edmond Norbert Landry, New Iberia, La.; Medical Department of Tulane University of Louisiana, New Orleans, 1911; member of the American Medical Association; for many years parish coroner; on the staff of the New Iberia General Hospital; died March 19, aged 62, of coronary thrombosis.

Isaac Newton Lear, Vandergrift, Pa.; Western Pennsylvania Medical College, Pittsburgh, 1896; died March 18, aged 82, of carcinoma of the prostate.

Carlton George Lee, Highland Falls, N. Y.; University of Alberta Faculty of Medicine, Edmonton, Alberta, Canada, 1925; member of the American Medical Association; served in the Canadian Air Force during World War I; served during World War II; died in the Veterans Administration Hospital, Castle Point, March 25, aged 57, of amyloidosis of the kidney, liver and spleen.

Edwin Lewis, Claremore, Okla.; Central Medical College of St. Joseph, Mo., 1903; died in February, aged 86.

Samuel Lichtenstein, Kecoughton, Va.; University of Georgia Medical Department, Augusta, 1912; died February 21, aged 57.

James Hugh McClelland, Livermore, Calif.; Cooper Medical College, San Francisco, 1912; died in the Veterans Administration Hospital December 18, aged 60.

Crawford Ward McCormick, Detroit; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1913; member of the American Medical Association; on the staff of Delray General Hospital; died March 24, aged 60, of coronary occlusion.

William Raymond McDannell, Los Angeles; the Hahnemann Medical College and Hospital, Chicago, 1905; died March 16, aged 74, of hypertensive heart disease.

Samuel James McDonald, Newton, Mass.; Harvard Medical School, Boston, 1901; member of the New England Ophthalmological Society; served as an examiner for the draft board during World Wars I and II; for many years affiliated with St. Elizabeth's Hospital and the Massachusetts Charity Eye and Ear Infirmary in Boston; died March 28, aged 74, of cerebral thrombosis.

Allister Francis MacDougall Jr., Stillwater, Okla.; Boston University School of Medicine, 1944; certified by the National Board of Medical Examiners; served during World War II; died March 14, aged 28.

George McIntyre, East Saugatuck, Mich.; Illinois Medical College, Chicago, 1904; also a graduate in pharmacy; served during the Spanish-American War and World War I; at one time practiced in Chicago, where he was medical inspector for the board of health and affiliated with Ravenswood and St. Elizabeth's hospitals; died March 30, aged 75, of myocarditis.

Edwin Everett Madden, Forest Park, Ill.; Reliance Medical College, Chicago, 1909; died in March, aged 72.

Jesse Krekore Marden, Claremont, Calif.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1898; formerly a missionary in Turkey and Greece; died recently, aged 76.

Henry Louis Martin, Detroit; Detroit College of Medicine and Surgery, 1922; on the staffs of Providence Hospital and Holy Cross Hospital; died March 17, aged 58, of coronary occlusion.

Thomas Patrick Martin ⊕ Carbondale, Pa.; Medico-Chirurgical College of Philadelphia, 1905; served during World War I; fellow of the American College of Surgeons; on the staff of St. Joseph's Hospital; died March 13, aged 71, of acute cardiac failure.

Edward Joseph Meehan, Lowell, Mass.; Jefferson Medical College of Philadelphia, 1947; served a residency at St. John's Hospital; a veteran of World War II; died March 17, aged 26.

Angus Washburn Morrison ⊕ Wayzata, Minn.; Johns Hopkins University School of Medicine, Baltimore, 1910; formerly on the faculty of the University of Minnesota Medical School, Minneapolis; served during World War I; member of the American Psychiatric Association and the Central Neuropsychiatric Association; for many years on the staff of the Minneapolis General Hospital; died in Eitel Hospital, Minneapolis, recently, aged 65, of carcinoma of lung.

Charles Robert Nelson, Oakland, Calif.; Western Pennsylvania Medical College, Pittsburgh, 1895; member of the American Medical Association; on the staff of the Samuel Merritt Hospital; died February 27, aged 77, of arteriosclerosis and coronary occlusion.

William Henry Nix, Worthington, Pa.; Jefferson Medical College of Philadelphia, 1905; member of the American Medical Association; died recently, aged 73, of hypertension and coronary artery disease.

James Jarvis Parker ⊕ Elizabeth City, N. C.; Temple University School of Medicine, Philadelphia, 1939; on the staff of Albemarle Hospital; died March 27, aged 34, of coronary thrombosis.

George Floyd Phelps, Drexel Hill, Pa.; Jefferson Medical College of Philadelphia, 1907; served on the staffs of the Jefferson and Philadelphia General hospitals in Philadelphia, New Jersey State Hospital in Trenton, and the Pennhurst State School in Spring City; died March 10, aged 78, of hypertensive cardiovascular disease.

Minor Wallace Pitts ⊕ Luling, Texas; American Medical College, St. Louis, 1893; past president of the Caldwell County Medical Society; on the staff of the Luling Hospital; died March 20, aged 80, of coronary occlusion.

Clarence Virgil Porterfield, St. Clairsville, Ohio; Starling-Ohio Medical College, Columbus, 1913; president of the county board of health; member of the board of education; died March 17, aged 61, of pulmonary embolism.

Harry Blackburn Pryor, Ashland, Mo.; University of Louisville (Ky.) Medical Department, 1911; member of the American Medical Association; served overseas during World War I; died in March, aged 61.

Gail Kelvin Ridelsperger ⊕ Warren, Pa.; University of Buffalo School of Medicine, 1933; fellow of the American College of Surgeons; on the staff of Warren General Hospital; died March 15, aged 44.

Mary Caroline Reed Stratton, Denver; Northwestern University Woman's Medical School, Chicago, 1892; died March 19, aged 80, of coronary thrombosis.

George Ross Taylor ⊕ Akron, Ohio; Western Reserve University School of Medicine, Cleveland, 1924; member of the Summit County Board of Health; served on the staffs of the Wadsworth (Ohio) Hospital and the Citizens Hospital, Barberton; died February 6, aged 50, of coronary occlusion.

Thomas H. Turner, Auburn, Ky.; University of Tennessee Medical Department, Nashville, 1893; member of the American Medical Association; died in Princeton, Ind., March 18, aged 81.

Rufus Whitis ⊕ Dallas, Texas; Jefferson Medical College of Philadelphia, 1884; died February 22, aged 89.

Leslie Arno Yaeger ⊕ Trenton, N. J.; University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, 1921; served during World War I and World War II; school physician; affiliated with St. Francis Hospital, where he died February 28, aged 56, of hepatitis.

Louis Augustus Zerega di Zerega, Staten Island, N. Y.; College of Physicians and Surgeons, medical department of Columbia College, New York, 1889; died in Staten Island Hospital March 15, aged 84.

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Foreign Letters

TURKEY

(From Our Regular Correspondent)

ANKARA, April 19, 1949.

Treatment of Toxic Diffuse Goiter with Thiouracil and Methylthiouracil

Dr. Huseyin Salor of the Istanbul-Pera Municipal Hospital has published observations on 6 patients treated with thiouracil and methylthiouracil. The patients were between 28 and 42 years of age; 4 were women and 2 were men. All were suffering from thyrotoxicosis. The treatment was divided into two periods. During the first period the patients were given a daily dose of 0.30 to 0.40 Gm. thiouracil and 0.20 to 0.25 Gm. methylthiouracil for an average of two weeks. By this time the basal metabolism of all 6 patients and the cholesterine of the blood had become normal again. The feeling of oppression and other hyperthyroid symptoms had disappeared. This treatment had no effect on exophthalmia. Frequent blood examinations and leukocyte counts revealed no abnormalities. During the second period the patients were given a daily dose of 0.15 to 0.20 Gm. thiouracil and 0.05 to 0.10 Gm. methylthiouracil. This dosage was continued for two to three months. In 2 of the 6 patients symptoms of relapse appeared, and they were given another two weeks' treatment. Toxemia or idiosyncrasy symptoms were absent. The patients have been discharged and are being followed up to find out whether it will be necessary to repeat the treatment from time to time.

Fiftieth Anniversary of the Gülhane Hospital

The Gülhane Hospital at Istanbul-Sarayburnu was established in 1898 by Dr. Rieder Pasha. The medical students graduating from the Military Academy Medical School with the rank of captain were required to attend there a one year theoretic and practical course followed by another examination. Drawing lots, they were then assigned to their respective positions. Those having passed the examination with the highest marks were retained at the acadamy as assistants and instructors. The Gülhane Hospital, which has always held a high place in the esteem of the Istanbul population, continued to function there until 1939, when it was transferred to Ankara. Several of the clinics of this 500 bed hospital now serve as teaching units of the Ankara University medical school.

On the occasion of the fiftieth anniversary of the hospital a ceremony was held on Dec. 30, 1948. It was attended by Ismet Inönü, President of Turkey; Dr. Kemali Bayazit, the Minister of Health and Social Assistance; the Minister of National Defense and other cabinet members, prominent army and civilian members of the medical profession.

Custom-Free Drugs

The bill introduced by the Ministry of Health and Social Assistance proposing the custom-free importation of vital remedies and chemicals has passed the National Assembly and became law. Streptomycin, insulin and the like, the high price of which (5 to 7 Turkish pounds per gram in the pharmacies) often was prohibitive, will now be available for 2.8 to 3 liras—about $11—per gram. In many cases of tuberculous meningitis treatment with streptomycin had to be abandoned because parents could not afford to pay the high price and the hospital did not have sufficient funds to provide the drug free. The rising cost of living during and after the wear has greatly increased the number of tuberculous patients. This reduction in price will enable government hospitals to provide these important remedies free of charge for patients unable to pay for them. The new law also provides for custom-free importation and tax exemption for DDT, which has proved effective in malaria control work. Though in 1948 there have been no malaria epidemics, the malaria morbidity rate was greatly reduced in the malaria areas and there have been no deaths there due to malaria. The new law also contains a provision for customs and tax exemption for vitally important remedies that may be discovered in the future.

Death of Prof. Akil Muhtar Özden

Prof. Akil Muhtar Özden, who for thirty-seven years taught at the Istanbul University Medical School, died March 12 after a long illness. Like many medical students and physicians who, under the autocratic rule of Sultan Abdul Hamid II, had to leave the country because of their leanings toward democracy, Akil Muhtar, while still an undergraduate at the military medical school, fled to Switzerland, where he continued his medical studies and was graduated from Geneva University. After the declaration of the constitution in 1908 Dr. Akil Muhtar returned to Istanbul to become professor of hygiene at the Istanbul Civil Medical School; in 1909 he became professor of pharmacodynamics and clinical therapy of the Istanbul University Medical Faculty. He had one hundred and fifty-six publications in the Turkish and one hundred and two in the French language to his credit. He was a member of seven foreign medical societies. Prof. Akil Muhtar for many years served as vice president of the Turkish Red Crescent Society and took part in the international Red Cross Congress. His textbooks on pharmacodynamics and those on treatment have had a great many editions. At his Istanbul consulting rooms he was the most sought after authority on internal diseases; he was also advisory physician to President Ismet Inönü.

ISRAEL

(From Our Regular Correspondent)

JERUSALEM, April 22, 1949.

Medical Faculty of the Hebrew University in Jerusalem

The Medical Faculty of the Hebrew University in Jerusalem will be established soon. It has grown from the Institute of Microbiology, which was provided by the American Jewish Physicians' Committee and which was functioning before the University was opened in 1925. Other departments eventually were created, until there were available all courses necessary for premedical studies.

In 1936 the University and the Hadassah Zionist Organization of America agreed to undertake the establishment of a medical faculty in the Hebrew University. The Hadassah was to provide a modern hospital and facilities for teaching clinical subjects, and the University the preclinical education. The hospital now is known as the Hadassah-Rothschild University Hospital. Senior clinical appointments were to be made after consultation between Hadassah and the university, who were to be advised by a board of American authorities eminent in medical education.

Some of the preclinical departments are in need of expansion, and plans for enlargement were undertaken before the outbreak of recent hostilities. While some building was undertaken during hostilities, the preclinical departments still in need of expansion are bacteriology and hygiene, parasitology, physiology and pathologic chemistry, experimental pathology and cancer research, and radiobiology.

The hospital beds were to be increased from 300 to 500, and a hospital for tuberculosis for teaching was to be erected,

but this building program also was interrupted. Eventually the school will provide a six year course, of which two years will be devoted to premedical subjects. A year of internship will be obligatory. About 50 students will be admitted each year to the school. In time a dental faculty and a college of pharmacy will be added to the school.

Because of the shortage of scientific personnel, the personnel of the medical school will be recruited in part from persons in Israel and abroad and from younger members of the staff who will be sent to the United States for further training. A number of the latter already have been sent to the United States. In spite of the handicaps, the university has had considerable teaching experience. Many of its graduates hold responsible governmental and civilian positions. Furthermore, many have received postgraduate clinical training.

The Jerusalem Society for Internal Medicine

A Society for Internal Medicine was founded in Jerusalem in March 1949. This society was formed as a result of a proposal made at the International Congress for Internal Medicine held in Basel in September 1948. At the Basel meeting it was suggested that an international organization of the societies for internal medicine be formed.

ITALY

(From Our Regular Correspondent)

FLORENCE, April 15, 1949.

Course on International Medical Ethics

The Surgeon General of the Belgian Army, Dr. J. Voncken, Secretary General of the International Committee on Military Medicine and Pharmacy, presented four lectures on international medical ethics at the School of Military Health in Florence. General Voncken discussed military medicine at the national and international levels, the history of the humanitarian movement and the international judicial situation of the physician. The chancellor of the University of Florence has invited General Voncken to hold an analogous course at the University of Florence next fall.

Oto-Neuro-Ophthalmologic Association

This association held its fourth international congress in Bologna. Meningoendocraniosis in ophthalmology was the subject of the first report presented by Professor Rubino of Florence. The speaker gave a brief summary of the general symptoms, such as headache, and endocrinodiencephalic, mental, olfactory and cochleovestibular disturbances. He discussed the various fundamental roentgenologic signs of the cranium and the ocular signs and symptoms which may be encountered in meningoendocraniosis. The lesion of the ocular fundus may involve the optic papilla and the central retinal vessels. There may be such functional symptoms as bitemporal hemianopsia referable to the upper quadrants, also called "chiasmal sign" or "small chiasmal syndrome," which may be of great localizing value in diagnosis.

Professor Bertolotti of Naples discussed the relationship between endocraniosis and deep perisinuitis.

Professor Porta of Siena discussed pontocerebellar arachnoiditis and meningoendocraniosis of the temporobasilar region; he stated that when this condition is secondary to chronic inflammatory processes of the mastoid it may induce symptoms which justify a parallelism with the forms described by Lunedei as sequelae of hyperergic chronic inflammatory processes at the base of the cranium, involving also the diencephalon.

The reports were followed by discussion in which many in attendance participated.

BRAZIL

(From Our Regular Correspondent)

RIO DE JANEIRO, April 27, 1949.

Virus of Brazilian Typhus in Milk

Dr. Octavio de Magalhães, of the Oswaldo Cruz Institute, was able to prove, as has been reported in previous letters, that the virus of Brazilian typhus can pass through the placenta of Macacus rhesus and infect the fetus, and can go through the apparently normal mucosa of the gastrointestinal tract of dogs causing the disease. Recently, Dr. de Magalhães was also able to demonstrate the presence of the virus in the milk of goats (Capra hircus), these animals being, as the same author pointed out in the past after careful experimentation, a very good reservoir of the Brazilian virus, as shown by the presence of the virus in blood and by a positive group Weil-Felix reaction of high titer, although without apparent disease. In many places of the interior of Brazil goats are a substitute for cows as a milk supply for children and adults, and in some districts goat's milk is even considered superior to cow's milk. Now, with the demonstration that the virus of Brazilian typhus may be present in goat's milk, and the proof that the virus is able to pass through the apparently normal digestive tract, it is easy to understand how infants living in strictly domestic environment can contract the disease, as Dr. de Magalhães has shown in several instances, even for very young infants.

Blood Types of Brazilian Indians

Dr. Ernani M. da Silva, of the Oswaldo Cruz Institute, and Drs. F. Ottensooser and R. Pasqualin, of the Laboratorio Paulista de Biologia, studied the blood of Caiuá and Bororo Indians of the state of Matto Grosso for the determination of the common blood groups, MN factors and Rh types. The blood of 356 Indians (237 Caiuás and 119 Bororos) revealed the 0 group in all of them. Among 134 Caiuás 79.9 per cent belonged to type M, 0.7 per cent to N and 19.4 per cent to MN. Among 173 Caiuás and 103 Bororos not even one negative Rh was found. The distribution of the Rh types in 135 Caiuás and 103 Bororos was almost identical: the average values were 22.7 per cent Rh_0, 19.3 per cent Rh_0, and 58.0 per cent Rh_1Rh_2 or Rh_x. American Indians are connected with Mongoloids by some serologic characteristics, such as an appreciable ratio of R^a and scarcity or lack of the Rh-negative type, but generally they also are distinguished within this ethnical group by high proportions of O, M and Rh_0. In Matto Grosso Indians these percentages are particularly high.

A Focus of Echinococcosis

After Iceland—the place where the incidence of hydatidosis is highest—Australia, Argentina and Uruguay are known as important foci of the disease, which is connected with cattle raising, abundance of dogs and poor habits of personal hygiene. Evidence is accumulating to prove that the state of Rio Grande do Sul, the southermost of Brazil and adjoining Uruguay, and also devoted to cattle raising, is another focus that must be taken into consideration. Dr. Darcy Xavier, of the Misericordia Hospital of Pelotas, a city of 80,000 population near the Uruguayan border, studied the records of the hospital, from 1918 to 1947, to find out the number of cases of hydatidosis attended at that institution and gather data about the patients and the disease. During the thirty year period, 196 cases of the disease were treated at the hospital, all the patients being residents of the rural districts around Pelotas, the present aggregate population of which is about 500,000. On the basis of this population at the midpoint of the period, this represents the average annual morbidity rate of 1.53 per hundred thousand. As would be

expected, the incidence varies with the individual districts: Arroio Grande 5.7, Pinheiro Machado 5.3, Piratiny 5.0, Pelotas 2.2, Palmar 2.1, Herval 1.7, Cangussú 1.0 and Jaguarão 0.8. The cases are almost evenly divided between the two sexes: 90 cases in males (45.9 per cent), and 106 in females (54.1 per cent). The age distribution of the patients was as follows: 0 to 9 years, 26 (13.3 per cent); 10 to 19 years, 54 (27.5 per cent); 20 to 29 years, 55 (28.1 per cent); 30 to 39 years, 33 (16.8 per cent); 40 to 49 years, 16 (8.2 per cent); 50 to 59 years, 9 (4.6 per cent); 60 to 69 years, 2 (1.0 per cent), and 70 to 79 years, 1 (0.5 per cent). The localization of the cysts was as follows: liver, 102 (52.0 per cent); lungs, 43 (21.9 per cent); diffuse abdominal form, 16 (8.2 per cent); orbit, 5 (2.5 per cent); muscles, 4 (2.0 per cent); retroperitoneal, kidney, mesentery and epiploon, 3 each (1.5 per cent each); pancreas, mammary gland and bladder, 2 each, ligamentum latum uteri, pleura, ductus choledochus, ovary, spleen, parotid mediastinum and iliac bone, 1 each.

Correspondence

HEALTH TEACHING BY PHYSICIANS

To the Editor:—One of the objectives of the American Medical Association which has been stressed a great deal lately is public health education. What may be a doctor's role in such a program? One of the finest avenues open is health teaching in a college or university. Our belated interest in public relations can receive impetus from this contact with the public, teaching hundreds of impressionable young students in a wholesome atmosphere away from the sickroom and office. Such an experience will be pleasurable and beneficial to all concerned.

There are many fields of health taught in a university in which the knowledge of the physician is invaluable. At the University of Utah last year, three thousand students in a student body of ten thousand took courses in health. Except for a few hundred in the field of school health education, all these students were taught by busy practicing physicians. It is with the idea in mind that a physician has an excellent opportunity to be of service to the public and to his profession that an outline of our major courses at the University of Utah is offered.

For forty years a course in personal hygiene has been required of all men and women at the University. Sections on personal hygiene are taught by physicians who spare the time year after year to come to the campus and teach. Occasionally the time is a costly sacrifice; nevertheless, these men and women have compensations beyond the honorarium offered. They value their university associations; above that, they feel that the contact with young people and the information given are worth while. Obviously, such information does not remain restricted to the student himself but is disseminated in ever widening circles to family, friends and community. At present, four men physicians and one woman physician are teaching about 1,300 men and women personal hygiene.

As a result of the furor raised about the physical defects found in recent selective military training health examinations, there is a strong tendency to require courses in personal hygiene in the higher institutions. This is an opportunity for physicians.

At the University of Utah another health course is unique and has commanded wide attention. It is labeled "Matrology," a word coined from the combination of "mater" and "ology", i. e., science of motherhood. It was started soon after World War I by a busy practitioner in Salt Lake City who felt that "university women should know more than factory women" about their bodies during oncoming motherhood. He taught them "what a doctor would like his daughter to know." Enrolment grew with the years and was limited to women until a demand from the men resulted in the establishment of "Patrology" in the spring of 1947.

Matrology and Patrology fill a popular demand and need. They are similar courses in obstetrics and pediatrics which stress the normal. Two thirds of the course is devoted to prenatal care, to human embryology, to common disturbances and complications of pregnancy and to the mechanics of normal labor. The film "Normal Labor" taken by De Lee at Chicago Lying-in Hospital climaxes this part of the course. The latter part is concerned with infant care in the first year. Matrology and Patrology are not required courses. Registration is entirely voluntary; yet 338 women and 815 men were enrolled last year —11½ per cent of the student body in one year.

These courses are taught by physicians, who not infrequently come directly from the delivery room to the lecture room. Their voices carry authority.

Evaluations of Matrology and Patrology are enthusiastic, from the students, parents, physicians and the University administration. Students who later become parents find the subject matter of inestimable value in allaying fears and preparing for parenthood. Boys and men particularly have been slighted in this field. Local physicians have been particularly impressed with the intelligence and cooperation of their women patients who have had Matrology. Comments are being made already on the cooperation and participation of the prospective fathers in conferences with the physician before and after birth of their babies. It is apparent that such courses in a university promote a good rapport between the medical profession and a very fine portion of our population.

Another course of value is entitled "interpretation of medical nomenclature." It is taken by those who plan to be in close association with the medical profession and with hospitals. These include student dietitians, physical therapists and social workers. A closely related course is that on "Medical Information for Social Workers." These subjects are taught by physicians.

Physicians from Salt Lake City have been most generous in devoting their time and knowledge to the academic field at the University. They are guest lecturers in courses in the areas of physical therapy, first aid and safety, school health education, preparation of health teachers, child development, mental hygiene, public health, courtship and marriage. The areas are wide into which physicians may enter.

Heretofore, too much health teaching has been left to poorly trained personnel. Physicians are always welcome in the health education field. More active and aggressive participation is recommended.

ALMA NEMIR, M.D., Salt Lake City.

ROENTGEN IRRADIATION FOR THYROTOXICOSIS

To the Editor:—The article in your April 16 issue by Robert H. Williams on selection of therapy for individual patients with thyrotoxicosis fails to accord roentgen irradiation the place it has established in the treatment of this disease.

The author's point that initial treatment with thiouracil is applicable in many cases is well taken. His frank comments on the complications and bad effects of this drug are to be commended. His impression that irradiation is best given by radioiodine is hardly supported by his statement that "the main drawback of this type of treatment is the difficulty involved in selecting the appropriate dosage, errors in which may either cause myxedema or permit the thyrotoxicity to persist. . . .

Radioiodine is distinctly less available throughout the country than are the other forms of therapy and, in the light of present information, it should remain so. Extensive use of it would pose a number of public health considerations." In view of the frank difficulties of administration and of dosage calculation, it would seem that the simpler and safer method of irradiation by external roentgen rays merited more prominence in the article, effective as it is in over 80 per cent of cases of diffuse toxic goiter. Myxedema is much less common after roentgen irradiation than after radioiodine.

Last, and by no means least, I concur with the author in the merits of thyroidectomy, especially in patients with a large nodular gland and in patients who have failed to respond to thiouracil and irradiation.

Intense attention to certain aspects of any problem commonly results in inattention to others, no matter how well established. The interest in radioactive isotopes in recent years has caused considerable neglect of simpler, safer and more available methods of irradiation.

L. H. GARLAND, M.D., San Francisco.

MEDICAL CARE OF THE INDIANS

To the Editor:—In two recent issues of THE JOURNAL have appeared special articles on the care of Indians in the Upper Midwest area and in the Navajo area. As I am at the present time a doctor in the Indian Service, I read these articles with considerable interest, and as I have worked for the Indian Service in Idaho and consequently know something of conditions in the Upper Midwest area, I am pleased to observe that the group who made that survey did an exceptionally fine piece of work. Both their findings and recommendations show considerable discernment and acumen. I am not familiar with the Navajo area and consequently am in no position to form an opinion of that report. I would be much interested, however, in a report on the area of Washington, Oregon and California, as I do know something of Indian conditions in these states and know that they differ somewhat from those of the Upper Midwest area.

Being a federal employee, I am not at present eligible to belong to a state or county medical society and consequently am not a member of the American Medical Association. Also being on a federal salary I am scarcely able at this time to contribute the entire $25 toward defeat of the vicious so-called health bill sponsored by Oscar Ewing and others. I am, however, enclosing a check for $10, which I hope will help a little in defeating this proposed legislation. I know at first hand what federal medicine does to a doctor, and I know what it does to patients.

C. W. DEWEY, M.D., Hoopa, Calif.

FREE ISOTOPES

To the Editor:—Students of the infiltration technic will be pleased at the latest evidence of how even the most erudite will fall for the Grecian gift.

In THE JOURNAL for April 16, page 1084, appears the heading "Expand Free Radioisotope Program." There then follows an explanation that the U. S. Atomic Energy Commission has announced that all isotopes are now free.

However, in the next paragraph it states that to finance the new program for its first year of operation $450,000 has been allocated. This is just for the first year. Time passes rapidly. Estimates are often inadequate. Is it not unreasonable to envisage that this free program is going to require allocations of perhaps $10,000,000 in the next ten years? Since when, then, is it free?!

It is readily granted that this program cannot be conducted or entirely subsidized by private enterprise. The Atomic Energy Commission is doing a good job. However, do not let us deceive ourselves. The radioisotope program is not free; it is expensive; we are all paying for it. May we suggest that you reprint this article and use the heading "Expand Costly Radioisotope Program." "NOTICE: All tax-payers kindly stand ready to pay at least $500,000 for the first year."

M. A. SISSON, M.D., San Francisco.

AN ALLERGY SURVEY

To the Editor:—The New Jersey Allergy Society has formed a committee on aerobiology to do an air survey of the state of New Jersey for the purpose of finding allergenic factors not presently recognized. The work will be done in the following fields: (1) pollen surveys, (2) bacteria surveys, (3) fungi surveys, (4) chemical contaminants and (5) meteorology.

With funds supplied by Schering Laboratories, six Wells air centrifuges will be set up in widely separated sites in the state. Daily air specimens will be studied. The chairmen for the entire project are Drs. Nathan Schaffer of East Orange, and Edward E. Seidman, of Plainfield. Subchairmen are as follows:

1. Pollen, Dr. L. Byck, Newark.
2. Bacteria, Dr. E. Seidman, Plainfield.
3. Fungi, Dr. N. Schaffer, East Orange.
4. Chemical contaminants, Dr. C. Weston, Glen Ridge.
5. Meteorology, Dr. F. Rosen, Newark.

The subcommittee on mycology, which consists of Drs. Schaffer, Seidman, Byck, Suesserman and Feldman, are attending conferences on mycology four hours a week at Rutgers University in New Brunswick, under the direction of Drs. C. M. Haenseler and B. H. Davis of the department of plant pathology, College of Agriculture. These conferences started with the school term in February, and plans are being made for their indefinite continuance. Drs. Haenseler and Davis will work with this committee in attempting to identify any fungi found in quantity. Extracts of these will be made and sent to all members of the society for clinical testing and evaluation.

Plans are being made to set up similar conferences in bacteriology and pollen identification in the near future.

NATHAN SCHAFFER, M.D.,
East Orange, N. J.

IT'S THE F. S. A.

To the Editor:—In regard to a Current Comment, THE JOURNAL, February 19, page 531, in addition to your observation concerning letterheads, you may be interested to know that even lantern slides made and issued by the National Cancer Institute for distribution throughout the United States in the fields of professional and lay education are stamped, at the bottom, so that all can read F. S. A.

In all innocence, during a preview of some of these slides which I saw at the National Cancer Institute, I inquired what F. S. A. meant. I was told it meant "Federal Security Agency," and then I asked why it wasn't N. C. I., National Cancer Institute. The answer was simply "Orders."

JAY MCLEAN, M.D., Arlington, Va.

Medical Examinations and Licensure

COMING EXAMINATIONS AND MEETINGS

NATIONAL BOARD OF MEDICAL EXAMINERS

NATIONAL BOARD OF MEDICAL EXAMINERS: *Parts I and II.* Various Centers. June 20-22, Sept. 12-14. *Part III.* June, various centers. Exec. Sec., Mr. E. S. Elwood, 225 S. 15th St., Philadelphia 2.

EXAMINING BOARDS IN SPECIALTIES

AMERICAN BOARD OF ANESTHESIOLOGY, INC. *Written.* Various Centers. July 15. *Oral.* Oct. 16-20. Sec., Dr. Curtiss B. Hickcox, 745 Fifth Ave., New York 27.

AMERICAN BOARD OF INTERNAL MEDICINE: *Written.* Oct. 17. Asst. Sec.-Treas. Dr. W. A. Werrell, 1 Main St., Madison 3, Wis.

AMERICAN BOARD OF NEUROLOGICAL SURGERY: *Oral.* Chicago, June 1949. Sec., Dr. W. J. German, 310 Cedar Street, New Haven, Conn.

AMERICAN BOARD OF OPHTHALMOLOGY: *Oral.* New York, June 11-15; St. Louis, Oct. 15-19; Boston, December. Sec., Dr. S. J. Beach, 56 Ivie Rd., Cape Cottage, Maine.

AMERICAN BOARD OF ORTHOPAEDIC SURGERY. *Part II,* New York City, Jan. 1950.: Final date for filing application for Part II is Aug. 15. Address: Sec.-Treas., Dr. Harold A. Sofield, Room 1856, 122 S. Michigan Ave., Chicago.

AMERICAN BOARD OF OTOLARYNGOLOGY: Chicago, Oct. 4-7. Sec., Dr. D. M. Lierle, University Hospital, Iowa City.

AMERICAN BOARD OF PEDIATRICS: *Written.* Under local monitors, June 24. *Oral.* Cleveland, Sept. 16-18; New York City, Oct. 21-23; Chicago, Dec. 9-11. Sec., Dr. John McK. Mitchell, 6 Cushman Road, Rosemont, Pa.

AMERICAN BOARD OF PLASTIC SURGERY: Examinations are given in June and November of each year in the home town of applicants. Sec., Treas., Dr. Louis T. Byars, 400 Metropolitan Bldg., St. Louis, Mo.

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY, INC. *Special Examination,* October. Place to be announced. Final date for filing application is July 15. December, New York City. Sec. Dr. F. J. Braceland, 102-110 Second Ave., S.W., Rochester, Minn.

AMERICAN BOARD OF SURGERY: *Written.* Various Centers, October 26. Final date for filing application is July 1. Sec., Dr. J. Stewart Rodman, 225 S. 15th St., Philadelphia.

AMERICAN BOARD OF UROLOGY: *Written,* December. *Oral and Clinical.* Chicago, Feb. 11-15. Final date for receipt of case histories is Sept. 1, 1949. Sec., Dr. Harry Culver, 7935 Sunnyside Road, Minneapolis 18, Minn.

BOARDS OF MEDICAL EXAMINERS

ALABAMA: *Examination.* Montgomery, June 28-30. Sec., Dr. D. G. Gill, 519 Dexter Ave., Montgomery.

ARKANSAS: * Little Rock, June 9-10. Sec., Dr. L. J. Kosminsky, Texarkana. *Eclectic.* Little Rock, June 9-10. Sec., Dr. C. H. Young, 1415 Main St., Little Rock.

CALIFORNIA: *Examination.* San Francisco, June 21-23. Sec., Dr. Frederick N. Scatena, 1020 N St., Sacramento.

COLORADO: * *Examination.* Denver, June 20-22. Sec., Dr. W. W. King, 831 Republic Bldg., Denver.

CONNECTICUT: * *Examination.* Hartford, July 1. Secretary to the Board, Dr. Creighton Barker, 258 Church Street, New Haven.

DELAWARE: Dover, July 12-14. Sec., Dr. J. S. McDaniel, 229 South State St., Dover.

FLORIDA: * *Examination,* Jacksonville, June 26-28. Sec., Dr. Frank D. Gray, 12 N. Rosalind Ave., Orlando.

GEORGIA: *Examination.* June 8-9, Atlanta and Augusta. *Reciprocity.* Atlanta, June. Sec., Mr. R. C. Coleman, 111 State Capitol, Atlanta.

GUAM: *Endorsement.* Agana, Last Friday of each month. Sec., Capt. C. K. Youngkin, Dept. of Public Health, Guam. % F.P.O., San Francisco, Calif.

HAWAII: * *Examination.* Honolulu, July 11-14. Sec., Dr. S. E. Doolittle, 881 S. Hotel St., Honolulu.

IDAHO: Boise, July 11-13. Sec., Miss Estella S. Mulliner, Bureau of Occupational Licenses, 355 State House, Boise.

ILLINOIS: Chicago, June 28-30. Superintendent of Registration, Mr. Fred W. Ruegg, Capitol Building, Springfield.

INDIANA: *Examination.* Indianapolis, June 21-23. Sec. Board of Medical Registration and Examination. Dr. Paul R. Tindall, 416 K. of P. Bldg., Indianapolis.

IOWA: * *Examination.* Iowa City, June 13-15. Sec., Dr. M. A. Royal, 506 Fleming Bldg., Des Moines.

KENTUCKY: *Examination.* Louisville, June 15-17. Sec., Dr. Bruce Underwood, 620 S. 3rd St., Louisville 2.

LOUISIANA: New Orleans, June 6-8. Sec., Dr. Roy B. Harrison, 1507 Hibernia Bank Bldg., New Orleans.

MAINE: Augusta, July 5-6. Sec., Dr. Adam P. Leighton, 192 State St., Portland.

MARYLAND: *Examination.* Baltimore, June 21-24. Sec., Dr. Lewis P. Gundry, 1215 Cathedral St., Baltimore. *Homeopathic.* Baltimore, June 14-15. Sec., Dr. John A. Evans, 612 West 40th St., Baltimore.

MASSACHUSETTS: *Written.* Boston, July 12-15. Sec., Dr. George L. Schadt, 413 E. State House, Boston.

MICHIGAN: * *Written.* Detroit and Ann Arbor, June 13-15. Sec., Dr. J. Earl McIntyre, 203 Hollister Bldg., Lansing.

MINNESOTA: * Minneapolis, June 21-23. Sec., Dr. Julian F. DuBois, 230 Lowry Medical Arts Bldg., St. Paul 2.

MISSISSIPPI: Jackson, June 21-22. Asst. Sec., Dr. R. N. Whitfield, State Board of Health, Jackson.

MISSOURI: *Examination.* St. Louis, June 8-10. Exec. Sec., Mr. John A. Hailey, Box 4, Jefferson City.

MONTANA: Helena, Oct. 3-5. Sec., Dr. Otto G. Klein, First National Bank Bldg., Helena.

NEBRASKA: * *Examination.* Omaha, June 6-8. Dir., Bureau of Examining Boards, Mr. Oscar F. Humble, 1009 State Capitol Building, Lincoln 9.

NEW HAMPSHIRE: Concord, Sept. 8-9. Sec., Dr. J. S. Wheeler, 107 State House, Concord.

NEW JERSEY: *Examination.* Trenton, June 21-24. Sec., Dr. E. H. Hallinger, 28 West State Street, Trenton 8.

NEW YORK: Albany, Buffalo, New York and Syracuse, June 28-July 1, Sec., Dr. Jacob L. Lochner, 23 South Pearl St., Albany.

NORTH CAROLINA: *Examination.* Raleigh, June 23-25. Sec., Dr. Ivan Proctor, 226 Hillsboro St., Raleigh.

NORTH DAKOTA: * *Written,* Grand Forks, July 5-7. *Reciprocity,* Grand Forks, July 8. Sec., Dr. C. J. Glaspel, Grafton.

OHIO: *Examination.* Columbus, June 15-18. *Endorsement,* Columbus, July 5. Sec., Dr. H. M. Platter, 21 W. Broad St., Columbus.

OKLAHOMA: * Oklahoma City, June 8-9. Sec., Dr. Clinton Gallaher, 813 Braniff Bldg., Oklahoma City.

OREGON: * *Examination.* Portland, July 7-9. *Reciprocity.* Portland, July 22. Exec. Sec., Mr. Howard I. Bobbitt, 609 Failing Building, Portland.

PENNSYLVANIA: *Examination.* Philadelphia and Pittsburgh, July. Acting Sec., Mrs. B. G. Steiner, 351 Education Bldg., Harrisburg.

PUERTO RICO: San Juan, Sept. 6-10. Sec., Dr. Luis Cueto Coll, Box 3717, Santurce.

RHODE ISLAND: * *Examination.* Providence, July 7-8. Chief, Mr. Thomas B. Casey, 366 State Office Bldg., Providence.

SOUTH CAROLINA: *Examination.* Columbia, June 27-29. *Endorsement,* Columbia, June 27-28, Aug. 1, Sept. 5 and Oct. 3. Sec., Dr. N. B. Heyward, 1329 Blanding St., Columbia.

SOUTH DAKOTA: * *Examination.* Pierre, July 19. Sec., Dr. G. J. Van Heuvelen, Capitol Bldg., Pierre.

TEXAS: *Examination.* Austin, June 16-18. Sec., Dr. M. H. Crabb, 209 Medical Arts Bldg., Fort Worth 2.

UTAH: *Examination.* Salt Lake City, July 13-15. Sec., Dept. of Registration, Miss Rena B. Loomis, 324 State Capitol Bldg., Salt Lake City.

VERMONT: Burlington, June 21-23. Sec., Dr. F. J. Lawliss, Richford.

VIRGINIA: *Examination.* Richmond, June 17-18. *Reciprocity.* Richmond, June 16. Dr. K. D. Graves, 631 First St., S.W., Roanoke.

WASHINGTON: * Seattle, July. Sec., Mr. Edward C. Dohm, Department of Licenses, Olympia.

WISCONSIN: * *Examination.* Milwaukee, June 28-30. Sec., Dr. C. A. Dawson, Tremont Bldg., River Falls.

WYOMING: Cheyenne, June 20. Sec., Dr. Franklin D. Yoder, Capitol Bldg., Cheyenne.

* Basic Science Certificate required.

BOARDS OF EXAMINERS IN THE BASIC SCIENCES

ALASKA: Feb. 1950. Sec., Dr. C. Earl Albrecht, Box 1931, Juneau.

ARIZONA: Tucson, June 21. Sec., Mr. Francis A. Roy, Science Hall, University of Arizona, Tucson.

COLORADO: *Examination.* Denver, June 1-2. Sec., Dr. Esther B. Starks, 1459 Ogden St., Denver.

CONNECTICUT: New Haven, June 11. Exec. Asst., State Board of Healing Arts, Miss Mary G. Reynolds, 110 Whitney Ave., New Haven 10.

FLORIDA: *Examination.* Gainesville, June 11. Sec., Mr. M. W. Emmel, University of Florida, Gainesville.

MICHIGAN: *Examination.* Detroit and Ann Arbor, Oct. 14-15. Sec., Miss Eloise LeBeau, 101 N. Walnut St., Lansing 15.

MINNESOTA: Minneapolis, June 7-8. Sec., Dr. Raymond N. Bieter, 105 Millard Hall, University of Minnesota, Minneapolis.

OREGON: Portland, June 18, Sept. 3 and Dec. 3. Sec., Mr. Charles D. Byrne, State Board of Higher Education, Eugene.

TENNESSEE: Memphis, July 8-9. Sec., Dr. O. W. Hyman, 874 Union Ave., Memphis 3.

WISCONSIN: Milwaukee, Sept. 24 and Dec 3. Sec., Prof. W. H. Barber, Ripon College, Ripon.

Bureau of Legal Medicine and Legislation

MEDICOLEGAL ABSTRACTS

Workmen's Compensation Acts: Patient not Personally Liable for Medical Fees.—In two recent cases the Supreme Court of North Carolina had occasion to consider the right of a physician to recover a fee directly from his patient when the patient is injured during the course of his regular employment.

In the case of Worley v. Pipes the plaintiff filed suit to recover a sum alleged to be due him from the defendant for medical services rendered following an accidental injury. From a judgment in favor of the plaintiff physician, the defendant appealed to the Supreme Court of North Carolina.

The defendant was injured by an accident arising out of his employment with a motor transport company, which company was subject to the provisions of the state workmen's compensation law. He accordingly went to his family physician, the plaintiff, for medical care and the plaintiff undertook to treat, and did successfully treat, the defendant for his injuries. At the time the medical services were rendered, neither the plaintiff nor the defendant knew that the case was compensable under the workmen's compensation law. The reasonable value of the services rendered by the plaintiff was $44, and the defendant made a token payment of $5 and impliedly agreed to pay the balance. Subsequently, the defendant, at his employer's suggestion, filed a claim under the workmen's compensation law and the Industrial Commission awarded him compensation, including the sum of $13.50 for medical services. When the defendant refused to pay the balance of $25.50, the present suit was filed.

The workmen's compensation law (General Statutes, section 97-90) provides:

(*a*) Fees for attorneys and physicians and charges of hospitals for services under this article shall be subject to the approval of the Commission; . . .

(*b*) Any person (1) who receives any fee, other consideration, or any gratuity on account of services so rendered, unless such consideration gratuity is approved by the Commission or such court, . . . shall be guilty of a misdemeanor, and upon conviction thereof, for each offense, be punished by a fine of not more than $500.00 or by imprisonment not to exceed one year, or by both such fine and imprisonment.

The defendant therefore contended that he did not owe anything personally because the foregoing section prohibited the payment of any fee not approved by the Industrial Commission. The plaintiff contended that if such is the effect of the foregoing provision then it is unconstitutional as being arbitrary, unreasonable and class legislation.

In addition to payment of compensation for an accidental injury arising out of and in the course of the employment, the workmen's compensation act provides that "medical, surgical, hospital and other treatment . . . shall be provided by the employer." The employer's liability for such medical, surgical, hospital service or other treatment required, when ordered by the Commission, shall, according to the act, be limited to such charges as prevail in the community for similar treatment of injured persons of a like standard of living when such treatment is paid for by the injured person. The act also provides that if the employer and injured employee failed to reach an agreement in regard to compensation, either party may make application to the Industrial Commission for a hearing in regard to the matters at issue and for a ruling therein, upon receipt of which application the Commission shall set a date for, and give notice of hearing. The Commission or any of its members shall then hear the matters at issue, determine the dispute, and make an award. There may be a review of the award by the full Commission, the superior court and the Supreme Court. Thus it is seen, said the Supreme Court, that the General Assembly has prescribed an adequate remedy by which any matter in dispute may be determined and settled.

The plaintiff makes it appear by his pleadings that the parties were subject to the workmen's compensation act and that he submitted his bill to the Industrial Commission and received approval for less than the full amount. It does not appear, however, that he asked for any hearings before the Commission or that he appealed the Commission's ruling. Under such circumstances, said the Supreme Court, the plaintiff is bound by the provisions of the act. Since the act provides that fees for physicians shall be subject to the approval of the Commission, and makes it a misdemeanor for anyone to receive any fee for services so rendered unless it be approved by the Commission, any promise made by the defendant-employee, to pay plaintiff the balance due on his account, is unenforceable and void. Consequently the trial court erred in finding for the plaintiff and the judgment in his favor was accordingly reversed.

In the case of Matros v. Owen, the plaintiff filed suit to recover a sum alleged to be due him from the defendant for medical services rendered following an accidental injury. From a judgment in favor of the plaintiff-physician, the defendant appealed to the Supreme Court of North Carolina.

The defendant was injured by an accident arising out of his employment as a mechanic for a company which was subject to the workmen's compensation law. The employer, thinking the injury was compensable under such law, directed the defendant to go to the plaintiff-physician for medical services. The reasonable value of the services rendered by the plaintiff was $25 and a bill in this amount was filed with the employer. Subsequently the employer and his insurance carrier denied liability, so the physician filed suit against the patient to recover the fee from him.

In addition to raising the same defense as was raised in *Worley v. Pipes*, the defendant contended that not withstanding the fact that the employer denied liability and refused to pay for medical treatment required by the defendant he, the defendant, who was not liable for such charges because the statute requires the employer to furnish medical attention even though the defendant was not entitled to compensation for the injury.

It does not appear, said the Supreme Court, that either party applied to the North Carolina Industrial Commission for a hearing in regard to the matter at issue and for a ruling thereon, as provided for in the workmen's compensation act, even though the plaintiff alleged and the court found that the parties were subject to, and had accepted the provisions of, such law. The remedy open to the defendant and to the plaintiff in respect to his bill for services rendered, said the Supreme Court, was to make application to the Industrial Commission and have it consider for approval the plaintiff's bill in the light of the provisions in the act. If the applicant be dissatisfied with the ruling of the Industrial Commission an appeal may be taken pursuant to the provisions therein stated. Under the facts alleged, the defendant is not indebted to the plaintiff for the services rendered, concluded the Supreme Court, and the judgment of the trial court in favor of the plaintiff was therefore reversed. *Worley v. Pipes, 50 S. E. (2d) 504 (North Carolina, 1948), Matros v. Owen, 50 S. E. (2d) 509 (North Carolina, 1948).*

Medical Motion Pictures

REVISED EDITION OF MOTION PICTURE REVIEWS NOW AVAILABLE

The Committee on Medical Motion Pictures has completed the first revised edition of the booklet entitled "Reviews of Medical Motion Pictures." It now contains all the film reviews published in THE JOURNAL, to Jan. 1, 1949. It also includes a classified table of contents as well as a list of motion pictures available through the Motion Picture Library, American Medical Association.

The purpose of the reviews is to provide a brief description and evaluation of motion pictures which are available to the medical profession. Each film is reviewed by competent authorities.

One copy has been mailed to the secretary of each county and state medical society. Additional copies are available on request from: Committee on Medical Motion Pictures, American Medical Association, 535 North Dearborn Street, Chicago 10.

Current Medical Literature

AMERICAN

The Association library lends periodicals to members of the Association and to individual subscribers in continental United States and Canada for a period of three days. Three journals may be borrowed at a time. Periodicals are available from 1938 to date. Requests for issues of earlier date cannot be filled. Requests should be accompanied by stamps to cover postage (6 cents if one and 18 cents if three periodicals are requested). Periodicals published by the American Medical Association are not available for lending but can be supplied on purchase order. Reprints as a rule are the property of authors and can be obtained for permanent possession only from them.

Titles marked with an asterisk (*) are abstracted below.

Alabama State Medical Assn. Journal, Montgomery

18:177-208 (Jan.) 1949

Program for Prevention of Deafness: First Year's Results at the Medical College of Alabama. G. E. Fisher and F. S. Moody.—p. 177.
Human Anaphylaxis: Report of Case Due to Sulfathiazole Sensitivity. C. R. Simmons.—p. 183.

Annals of Surgery, Philadelphia

129:1-160 (Jan.) 1949

Response to Parenteral Glucose of Normal Kidneys and of Kidneys of Postoperative Patients. D. R. Cooper, Vivian Iob and F. A. Coller. —p. 1.
*Appraisal of Oral Streptomycin as Intestinal Antiseptic, with Observations on Rapid Development of Resistance of E. Coli to Streptomycin. J. S. Lockwood, A. D. Young, McL. Bouchelle and others.—p. 14.
*Importance of Level of Lesion in Prognosis and Treatment of Carcinoma of Rectum and Low Sigmoid Colon. J. M. Waugh and J. W. Kirklin. —p. 22.
Malignant Tumors of Colon and Rectum. R. W. Postlethwait.—p. 34.
Management of Massive Gastroduodenal Hemorrhage. F. H. Amendola. —p. 47.
Experimental Study of Antiperistaltic Jejunal Loops. H. E. Pearse, M. Radakovich and C. L. Cogbill.—p. 57.
Sympathectomy in Peripheral Arteriosclerosis. E. E. Jemerin.—p. 65.
Tissue Reaction to Plastic Used in Surgery with Special Reference to Teflon. H. H. LeVeen and J. R. Barberio.—p. 74.
Experimental Pulmonary Collapse. J. L. Southworth.—p. 85.
Streptomycin in Surgical Infections. VII. Nonpulmonary Tuberculosis (Lymph Nodes, Urinary Tract, Bone, and Peritoneum). E. J. Pulaski, J. F. Connell Jr., A. Kowalczyk and S. F. Seeley.—p. 90.
Surgical Repair of Lacerations and Fistulas of Parotid Duct. H. A. Bailey and V. Skaff.—p. 103.
Acute Diverticulitis of Cecum: Report of 3 Cases Diagnosed Preoperatively as Acute Appendicitis. F. C. Henry.—p. 109.
Use of Full Thickness Skin Grafts in Repair of Large Herniae. R. J. Chodoff.—p. 119.
Primary Splenic Neutropenia: Specific Indication for Splenectomy: Report of Case. L. T. Paiumbo.—p. 131.
Unusual Metastatic Manifestations of Breast Carcinoma: III. Metastatic Involvement of Preauricular Lymph Nodes and Parotid Gland. Report of 5 Cases. J. B. Herrmann and F. E. Adair.—p. 137.
Bridging of Esophageal Defect by Pedicled Flap of Lung Tissue. R. Nissen. —p. 142.
Rupture of Subphrenic Abscess into Pericardium. N. C. Meyer.—p. 148.
Intraparotid Sebaceous Glands. C. M. Lee Jr.—p. 152.
Certain Anatomic Factors Related to Pathogenesis of Hemorrhoids: The Author's "Obliterative Suture" in Treatment of Small and Middle-Sized Internal Hemorrhoids. H. J. Fournier.—p. 156.

Oral Streptomycin as Intestinal Antiseptic.—Lockwood and his associates discuss the conflicting nature of reports on the oral administration of streptomycin in preparation for surgical treatment. They report 24 patients so treated and describe the methods used to obtain serial colony counts on the three groups of organisms studied, the coliform group, the streptococcus and the clostridia. Results obtained were inconsistent. Approximately half of the patients treated showed no response in the coliform group to orally administered streptomycin. About seven eighths of the patients showed no significant reduction in the number of streptococci present in the stool, and nearly two fifths of the cases showed no significant reduction in the number of clostridia present in the stool. Sensitivity titrations on the Escherichia coli group showed rapid development of resistance to streptomycin and brought out the fact that many strains of E. coli become able to proliferate in the concentrations of streptomycin which exist in feces. In a series of 9 cases in which treatment was with combined streptomycin and phthalylsulfathiazole results were also inconsistent. The authors conclude that the effect of orally administered streptomycin is unpredictable and unreliable, and its use in the preoperative preparation of surgical cases is not to be recommended.

Prognostic Location of Carcinoma of Rectum.—According to Waugh and Kirklin, the determination of truly comparable survival rates in patients undergoing combined abdominoperineal resection, and in those undergoing the other procedures which have arisen to challenge it, is not simple. The histologic grade of the lesion and its extent are factors which must be studied, but the location of the lesion, with respect to its distance from the anal margin, may also be important. The authors studied the effect of the level of the lesion on the prognosis in carcinoma of the rectum and the lower part of the sigmoid colon on 388 cases from the Mayo Clinic. It appeared that those patients whose lesions lie within approximately 5 cm. of the anal margin have a poorer prognosis than those whose lesions lie above this level. In order to obtain a more homogeneous group for analysis, the 248 cases in which the lesions showed grade 2 (Broders) malignancy were analyzed. These data show the same general trend as those of the entire group, but the differences are more clearcut. Patients whose lesions were within 5 cm. of the anal margin had a poorer prognosis than those with lesions lying higher up, and those with lesions lying 6 to 10 cm. removed from the anal margin had a poorer prognosis than those with lesions 11 cm. or more removed from this point. Considering only lesions with nodal involvement, a location 11 cm. or more removed from the anal margin allowed a much more favorable prognosis than did a lower location. The authors consider it unlikely that there is any inherent variation in the malignancy of adenocarcinomas at varying levels of the bowel and suggest that lateral spread beyond the line of resection carried out by the combined abdominoperineal operation is the probable explanation for the inferior prognosis in patients with lesions lying within 6 cm. of the anal margin.

Bulletin New York Academy of Medicine, New York

25:1-62 (Jan.) 1949

Use of Antiepileptic Drugs. H. H. Merritt.—p. 5.
Present Status of Liver Function Tests Including Observations on Newer Flocculation Procedures. M. Bruger and E. Oppenheim.—p. 16.
Review of Studies on Blood Sugar. E. T. Waters.—p. 32.

Endocrinology, Springfield

44:1-108 (Jan.) 1949

Effect of Androgen and Estrogen on Succinic Dehydrogenase and Cytochrome Oxidase of Rat Prostate and Seminal Vesicle. J. S. Davis, R. K. Meyer and W. H. McShan.—p. 1.
*Observations on Effects of Prepartal and Postpartal Estrogen and Progestrone Treatment on Lactation in Rat. S. M. Walker and J. I. Matthews.—p. 8.
Cholinergic and Adrenergic Components in Neurohumoral Control of Release of LH in Rabbit. C. H. Sawyer, J. E. Markee and B. F. Townsend.—p. 18.
Effects of Testosterone Propionate upon Sexual Libido and Production of Semen and Sperm in Rabbit. P. Cheng and L. E. Casida.—p. 38.
Response of Thyroid Gland in Normal Human Subjects to Administration of Thyrotropin, as Shown by Studies with I^{131}. M. M. Stanley and E. B. Astwood.—p. 49.
Transport of Progesterone in Blood. C. W. Hooker and T. R. Forbes. —p. 61.
Effect of Growth Hormone on Inorganic Phosphorus Levels in Plasma. Choh Hao Li, I. Geschwind and H. M. Evans.—p. 67.

Effect of Estrogen and Progesterone on Lactation.—Walker and Matthews made observations on the effects of antepartum and postpartum administration of estrogens, of progesterone and of combinations of estrone and progesterone on lactation in intact and in ovariectomized rats, using the growth rate of nursing young to indicate the rate of milk secretion. Daily (200 micrograms) treatment with estrone or diethylstilbestrol dipropionate begun on the second day of lactation does not inhibit milk secretion in ovariectomized rats, while moderate daily (5 micrograms and 10 micrograms) injection of estrone inhibits lactation in intact rats, the inhibition appearing ten to twelve days after the beginning of treatment. The inhibition of lactation induced by treatment with still larger dosage (1 mg.) of diethylstilbestrol dipropionate both in intact and in ovariectomized rats was accompanied by loss of weight of the mother and is interpreted as a toxic effect. Antepartum injection of estrone does not prevent the initiation of lactation either in ovariectomized (25 micrograms) or in intact (25 micrograms and 100 micrograms) rats but does produce a delayed depression in intact animals. Daily treatment with progesterone begun

before (2.5 mg.) or after (5 mg.) parturition neither prevents nor inhibits lactation. Simultaneous injection of estrone and progesterone begun before or after parturition does not prevent lactation but does inhibit established lactation aften ten to twelve days of treatment. The proliferation of the mammary glands showing inhibition of lactation suggests that stimulation of mammary growth by combined action of estrone and progesterone plays a role in the inhibition of milk secretion in the rat.

Journal of Thoracic Surgery, St. Louis

17:723-866 (Dec.) 1948

*Decortication of Nonexpandable Postpneumothorax Tuberculous Lung. D. A. Mulvihill and R. Klopstock.—p. 723.
Vagus Nerve Section in Treatment of Peptic Ulcer: Abdominal Versus Thoracic Approach. J. A. Weinberg, G. W. Campbell and R. B. Voelker.—p. 743.
Exploratory Thoracotomy in Management of Pleural Empyema. P. W. Sanger.—p. 756.
*Strangulation of Stomach and Traumatic Diaphragmatic Hernia. D. J. Dugan and P. C. Samson.—p. 771.
Traumatic Chylothorax: Review of Literature and Report of Case Treated by Mediastinal Ligation of Thoracic Duct. R. S. Lampson.—p. 778.
Combined Nitrous Oxide, Pentothal Sodium Anesthesia in Thoracic Surgery. W. A. Hudson and W. G. Mackersie.—p. 792.
Angiographic Study of Form and Function of Remaining Lung After Pneumonectomy. H. Neuhof and R. A. Nabatoff.—p. 799.
Gastric Cyst of Mediastinum. A. A. Ehler and Susanna Atwell.—p. 809.
Solitary Xanthoma of Lung. H. W. Scott Jr., A. G. Morrow and T. P. B. Payne.—p. 821.
Report of Case of Localized Bronchopulmonary Moniliasis Successfully Treated by Surgery. A. Hurwitz and R. Yesner.—p. 826.
Constrictive Pericarditis with Obstruction of Pulmonary Veins. W. Lawrence Jr., W. E. Adams and D. E. Cassels.—p. 832.
Primary Lymphosarcoma of Lung. H. C. Maier.—p. 841.
Complete Disruption of Esophagus: Report of Case. J. F. Higginson and O. T. Clagett.—p. 846.

Decortication of Nonexpandable Tuberculous Lung.—Mulvihill and Klopstock reasoned that pulmonary decortication used in the treatment of fibrosing traumatic hemothorax during the war might be applicable to some of the problems of pulmonary tuberculosis. They present the case material on the early results of an attempt to apply the basic principles of pulmonary decortication to postpneumothorax nonexpandable tuberculous lung. The indication for decortication in the first case was obliteration of the pleural dead space resulting from a postpneumothorax nonexpandable lung and its accompanying recurrent effusions. It was hoped that this would avoid a multiple stage deforming thoracoplasty. The result to date has been most satisfactory. In the second patient the object of decortication and reexpansion was to achieve sufficient increase in functional capacity to permit a permanent collapsing operation urgently indicated for cavity closure on the contralateral side. The procedure was successful. In the third patient obliteration of the right pleural space after artificial pneumothorax of fourteen years was achieved. The patient was relieved completely of symptoms of tension and dyspnea and stated that breathing was easier. He was relieved of the necessity of periodic refills and thoracenteses for recurrent fluid. He has been able to work at his profession as a commercial artist. The fourth patient presented a classical indication for decortication of a nonexpandable lung. The tuberculous process seemed to have been arrested for over seven years. The cause of the nonexpandability seemed to be chiefly the constricting fibrous coating of the pleura due to the chronic pneumothorax. The successful surgical reexpansion spared the patient an extensive thoracoplasty. The fifth case in this series represents a failure which was probably due to severe parenchymal fibrosis of the collapsed lung. So far there has been no clinical or roentgen evidence of reopening of cavities or reactivation of tuberculosis in the reexpanded lungs. Pulmonary decortication appears to be a useful procedure for dealing with the postpneumothorax nonexpandable lung.

Strangulation of Stomach and Diaphragmatic Hernia.—Dugan and Samson report 2 cases of traumatic diaphragmatic hernia with acute strangulation of the stomach. In both instances the diagnosis was made preoperatively, surgical treatment was performed transthoracically, the stomach was the only abdominal viscus involved and successful repair was obtained. Both cases occurred in young men in the military service, and occurred after dietary indiscretion. In neither patient had the diagnosis of hernia been made prior to the acute illness. A review of the literature revealed 4 similar cases with a mortality of 75 per cent. The authors conclude that all traumatic diaphragmatic hernias should be repaired as soon as the diagnosis is made and certainly before signs of obstruction occur. The transthoracic approach is the method of choice in the repair of hernias of this type.

Maine Medical Association Journal, Portland

39:339-384 (Dec.) 1948

*Boric Acid—Poison. A. W. Fellows, J. S. Campbell and R. C. Wadsworth.—p. 339.
Pathology and Therapy of Frost-Bite. R. C. Wadsworth and B. V. Whitney.—p. 345.
Electroshock Therapy: Survey of 171 Cases Treated in Private Practice. A. P. Stebbins.—p. 351.
Unusual Case of Foreign Body. J. E. Whitworth. —p. 356.
*Ephedrine and Nocturia. M. A. Vickers.—p. 358.
Less Sodium and More Water. W. B. Manter.—p. 359.
Carcinoma of Prostate Today. J. Memmelaar.—p. 361.
Treatment of Postoperative Pulmonary Atelectasis. C. S. Dwyer and H. J. Crocker.—p. 362.

Boric Acid, a Poison.—Fellows and his associates say that in the past two years at the Eastern Maine General Hospital 3 deaths have occurred in which boric acid poisoning had been suspected. In the first case chemical analyses of the tissues obtained at autopsy failed to reveal the presence of boric acid or other compound of boron. In the second case small amounts of boric acid were recovered from the brain and liver. In the third case large amounts of boric acid were recovered from both the brain and liver. Boric acid is ineffective as a bacteriostatic and bacteriocidal agent. The manifestations of boric acid poisoning are erythema of the skin followed by exfoliative dermatitis, exfoliative ileitis, hemorrhagic papillary edema of the bladder mucosa and degenerative changes in the central nervous system. Large doses of boric acid produce a severe state of shock. The authors are of the opinion that boric acid should be recognized as a dangerous poison and eliminated from the Pharmacopoeia.

Ephedrine and Nocturia.—Vickers stresses that in male patients with nocturia caution is necessary in the use of ephedrine. These patients should be forwarned that they should stop this medicine in the event of an increase in nocturia. The author cites several cases to illustrate this; when the ephedrine was withdrawn from these patients their nocturia returned to its previous status.

New England Journal of Medicine, Boston

239:1021-1060 (Dec. 30) 1948

Early Neurosyphilis. I. Kopp.—p. 1021.
Hospital and Health-Center Facilities in Massachusetts. The Massachusetts State Plan for Administration of Public Law 725 (Hospital Survey and Construction Act). V. A. Getting, A. D. Rubenstein and Claire F. Ryder.—p. 1028.
*Pneumococcal Pneumonia Treated with Aqueous Penicillin at Twelve-Hour Intervals. P. A. Tumulty and G. Zubrod.—p. 1033.
*Use of Testosterone in Treatment of Depressions. M. D. Altschule and K. J. Tillotson.—p. 1036.
Pollen Sensitivity in 100 Asthmatic Children. L. W. Hill.—p. 1039.
BAL (Concluded). R. V. Randall and A. O. Seeler.—p. 1040.
Chronic Rheumatoid Arthritis, Amyloidosis of Liver, Spleen, Kidneys and Adrenal Glands. Pericarditis, Acute Fibrinous, Probably Uremic. —p. 1047.
Coronary Thrombosis with Myocardial Infarction. Multiple, Massive Pulmonary Infarcts.—p. 1051.

Aqueous Penicillin at Twelve Hour Intervals in Pneumonia.—Tumulty and Zubrod report observations on patients with pneumococcic lobar pneumonia. Among these were 79 who were treated with aqueous penicillin G solution given intramuscularly every twelve hours, 69 received aqueous solution of penicillin intramuscularly every three hours and 58 were given penicillin in oil and beeswax. The patients who were treated with aqueous penicillin G solution, 300,000 units intramuscularly every twelve hours, fared as well as those on the usual schedules of administration. The authors regard the intramuscular administration of 300,000 units of aqueous penicillin G solution every twelve hours as the treatment of choice for pneumococcic lobar pneumonia.

Testosterone in Treatment of Depressions.—Altschule and Tillotson say that the injection of testosterone has been known to cause remission in male patients with depressions. The rationale for this treatment in the past has been that of

a replacement therapy in men past middle life. The fact that small doses are ineffective should have suggested the inadequacy of this concept. Some of the effects of the injection of steroid hormones resemble those caused by electroconvulsive therapy; these include fall in the plasma protein level, decrease in lymphocytes, reduction in eosinophil count, increased diuretic response to water and evidence of extracellular retention of water and sodium. The administration of desoxycorticosterone and of progesterone having failed to cause remission of mental symptoms, it was decided to use testosterone; all three of the hormones mentioned have the effect of causing salt and water retention, but only the last has an additional marked anabolic action. Thirty-one patients with the depressed phase of the manic-depressive psychosis, with involutional psychoses with depression, with reactive depressions and, in 1 case, schizophrenia with a strong depressive component were given testosterone intramuscularly in doses of 50 mg. daily for two or three weeks. The administration of testosterone in large doses was followed by remission of mental symptoms in all types of depression. The hormone acts apparently not as a specific sex hormone but as a substance with strong anabolic effects. In some patients the effects of electroshock and of testosterone are interchangeable, a phenomenon that suggests that the favorable effects of electroshock therapy are reparative and not destructive.

New York State Journal of Medicine, New York

49:1-112 (Jan. 1) 1949

*Bacterial Filtrates and Autogenous Vaccines in Treatment of Chronic Sinus Disease and Other Chronic Respiratory Affections: Preliminary Report. H. M. Kinghorn, G. E. Wilson and M. Dworski.—p. 41.
Blood Pressure Reaction of Patients Undergoing Eye Operations Under Local Anesthesia. W. G. Frey.—p. 46.
Reconstruction of Thumb. W. C. Graham and D. Riordan.—p. 49.
The Physician and Detection of Presymptomatic Cancer. S. W. Westing. —p. 51.
*Relief of Peripheral Vascular Pain and Angiospasm by Interlaminar Rhizotomy. J. H. Siris and J. W. Kahn.—p. 55.
New Ways of Influencing Intraocular Pressure. F. W. Stocker.—p. 58.
Physical and Roentgenologic Findings in Early Diagnosis of Nonopaque Foreign Bodies of Bronchial Tract. A. Q. Penta.—p. 64.
Present Status of Fenestration Operation. J. M. Smith.—p. 69.
Tuberculous Fistula. L. S. Knapp.—p. 73.

Treatment of Respiratory Diseases.—Kinghorn and his co-workers administered autogenous bacterial filtrates and vaccines to 47 patients with various chronic respiratory conditions. Twenty-three of these patients had lung disease and 24 had chronic nasal and accessory sinus troubles. Of the 23 patients with lung disease, 1 had bronchiectasis, 2 had chronic allergic bronchitis and 20 had far-advanced pulmonary tuberculosis. The patients were given the vaccines and bacterial filtrates intracutaneously into the forearm, vaccine into one arm and bacterial filtrate into the other, and with each successive dose alternating from one to the other arm. The injections should begin with small doses, 0.05 cc. of both bacterial filtrate and vaccine, and each week the doses can be increased by 0.05 cc. until 1 cc. of each preparation is reached. The first dose of 0.05 cc. vaccine should contain approximately 200,000,000 organisms. Injections should be given once a week, and treatment continued from four to six months. To the patients with chronic sinus diseases the bacterial filtrate solutions were also put directly into the sinuses when necessary and were always applied directly on swabs into the middle nares. The patient with bronchiectasis did not improve. The 2 patients with chronic allergic bronchitis improved, and 6 of the 20 patients with far-advanced pulmonary tuberculosis improved. Of the 16 patients with sinus disease, 6 were cured, 13 were improved or cured and 3 were failures. All the 8 patients with chronic nasal catarrh were improved and 3 of them were cured. Staphylococcus aureus was present in all 24 patients with sinus diseases and chronic nasal catarrh. Follow-up for one to thirteen years of the 20 patients with pulmonary tuberculosis revealed that of the 6 who improved 4 are living and well. One other patient is dead. One other has improved but is still under treatment. Of the 14 patients who did not improve with this treatment, 6 are living and 8 are dead.

Relief of Peripheral Vascular Pain.—Siris and Kahn treated 2 men aged 60 and 46, with intractable peripheral vascular pain, by interlaminar rhizotomy. A spinal anesthesia vasomotor test performed on the first patient three months before the rhizotomy showed definite evidence of organic vascular occlusive disease involving both lower extremities, more pronounced on the right side. A right lumbar sympathectomy with excision of the second and third lumbar ganglions relieved the radiating pain in the limb, but severe pain still persisted in the right first toe about the site of a gangrenous process in the ungual region. Because of the persistence of pain a posterior rhizotomy of the right fourth and fifth lumbar roots was carried out. Following intervention the pain was appreciably less. Two months after the operation healing of the great toe was noted. Apart from a slight weakness of dorsiflexion of the right foot no demonstrable limitation of motor power was observed. The second patient presented decided edema of the right foot, ankle and lower leg. A dry gangrenous plaque was present on the plantar surface of the first right toe and an infected gangrenous fissure at the base of the right fifth toe. Paravertebral sympathetic block at the first to fourth lumbar vertebrae was carried out on three occasions with immediate but only temporary relief. To effect permanent relief of the patient's pain the posterior roots of the fifth lumbar and the first sacral nerves on the right side were sectioned under spinal anesthesia. This resulted in considerable relief of the pain in the patient's toes, associated with hypesthesia corresponding to the dermatomes of the sectioned roots. There was no evidence of foot drop or other motor weakness. Three months after the operation the patient was able to resume his work as a car washer in a garage without pain or discomfort in the foot. It was felt that the procedure possibly spared each of these patients an amputation. It appears that relief of angiospasm in these cases, apart from the associated relief of pain, is attributable to abolition of the vasospastic reflex evoked by the pain factor.

Public Health Reports, Washington, D. C.

64:1-40 (Jan. 7) 1949

*Tuberculosis Control Program of Nine California Mental Institutions: Results of Initial Chest X-Ray Survey. W. R. Oechsli.—p. 4.
*Tuberculin, Coccidioidin, and Histoplasmin Sensitivity in Relation to Pulmonary Calcifications: Survey Among 6,000 Students at University of Chicago. W. G. Beadenkopf, C. G. Loosli, H. Lack and others.—p. 17.

Tuberculosis in Mental Institutions.—According to Oechsli, roentgen survey of general hospital patients is recognized as a productive field for tuberculosis case finding; mental institutions provide an even more productive field of investigation. A tuberculosis death rate of over 600 per 100,000 resident population in seven California hospitals for the mentally ill, and a death rate of nearly 400 per 100,000 resident population in two institutions for the mentally defective indicated the same need in California as in other states for an effective program of case finding and tuberculosis control. A prevalence of 8.25 per cent of previously unsuspected reinfection type pulmonary tuberculosis was discovered among 25,914 patients in seven mental hospitals. Prevalence of tuberculosis was higher among patients with dementia precox than among those with other mental conditions. This is probably because patients with dementia precox stay in the hospital longer and therefore have greater opportunity for exposure. A program of segregation was put into effect. All patients with active pulmonary disease were segregated; also, some of the patients with questionably active or potentially communicable disease. Patients with inactive disease were left on nontuberculous wards but checked periodically by roentgen ray. Among employees of mental hospitals there was a prevalence of 2.7 per cent pulmonary tuberculosis. The prevalence of reinfection type pulmonary tuberculosis in two institutions for the mentally defective was 1.2 per cent, much lower than among mentally ill patients. This difference is attributed to the younger age at which the mentally defective are admitted. Among employees in institutions for mentally defective persons the prevalence was 1.4 per cent.

Tuberculin, Coccidioidin and Histoplasmin Sensitivity in Relation to Pulmonary Calcifications.—Beadenkopf and his associates say that in view of the evidence that histoplasmosis and coccidioidomycosis may be etiologically associated with pulmonary calcification these antigens were included among the skin tests given as part of the tuberculosis control program

at the University of Chicago. Only 30 per cent of the students enrolled come from Chicago and vicinity; the greater number are drawn from practically all parts of the United States, and several hundred are from foreign countries. The present report is based on the study of 6,000 students registered at the University from January 1 to October 1947. This study on a population of diverse origin confirms the results of other recent surveys. It was found that (1) the prevalence of tuberculin sensitivity progressively increased from 10 per cent among the youngest age group to 57 per cent among those 50 years of age; (2) the rate of histoplasmin sensitivity began at 10 per cent among the youngest group and reached 38 per cent in the oldest group; (3) pulmonary calcifications were associated with histoplasmin sensitivity twice as frequently as they were with tuberculin sensitivity, and (4) the prevalence of both histoplasmin sensitivity and pulmonary calcifications was highest in the Lower Mississippi Basin of the United States.

Quarterly J. of Studies on Alcohol, New Haven, Conn.

9:329-514 (Dec.) 1948

Alcohol Tolerance in Individuals with Chronic Producer-Gas Intoxication. K. Bjerver and L. Goldberg.—p. 329.
*Motivational Pattern of Drinking: Based on Verbal Responses of Cross-Section Sample of Users of Alcoholic Beverages. J. W. Riley Jr., C. F. Marden and Marcia Lifshitz.—p. 353.
Importance of Cooperation of Physicians in Attack on Alcoholism. J. A. Höjer.—p. 363.
Proposal of Swedish Government Committee for Reform of Care of Inebriates. D. Wiklund.—p. 372.
Ancient Experience with Intoxicating Drinks: Non-Classical Peoples. A. P. McKinlay.—p. 388.

Motivational Pattern of Drinking.—Riley and his associates say that as a result of a nationwide survey of public attitudes concerning the drinking of alcoholic beverages data were acquired which support three hypotheses related to motivation for drinking. In the first place, they suggest the feasibility of applying standard analytic procedures to this aspect of the problem of consumption of alcoholic beverages. Secondly, the data lend powerful support to the hypothesis that drinking is as directly motivated by the influence of social pressures as it is by acquired inner drives. Thirdly, the relative weight of external social pressures versus inner acquired drives varies widely between different classes of drinkers. Direct social pressure is much more influential in motivating the drinking of women compared with men; the young compared with the old, and the occasional or infrequent compared with regular drinkers. On the other hand, regular drinkers tend to state that their reasons for drinking lie more within themselves than in the pressures from the group. Discussing the question of prevention, the authors cite among others an admonition emphasized by the National Committee for Education on Alcoholism; "Never insist on any one taking a drink." The effect of instituting such a small change in fashion, for example, as the serving of both alcoholic and nonalcoholic beverages at gatherings, and in such a manner that either choice seems appropriate might be far reaching. Certainly for the alcoholic addict who has regained his sobriety it would have significance, for he knows that he must not take one drink. In addition, there are those adults who do not like to drink, or have been ordered not to drink, but "choke it down just to be sociable." Finally, and probably of greatest significance, are the younger persons who have not yet accepted the view that drinking always goes with sociability.

Southern Surgeon, Atlanta, Ga.

14:801-862 (Dec.) 1948

Experiences with Total Gastrectomy. H. K. Ransom.—p. 801.
*Primary Carcinoma of Gallbladder. L. J. Gariepy and L. W. Gardner.—p. 820.
Conservative and Surgical Management of Esophageal Obstruction. G. E. Fisher and J. J. Hicks.—p. 829.
Placenta Previa with Report of 2 Cases. R. Mundt.—p. 841.
Inguinal Hernioplasty: Anatomic Evaluation of Current Methods. W. G. Whitaker Jr.—p. 847.

Primary Carcinoma of the Gallbladder.—The 19 cases of carcinoma of the gallbladder reported by Gariepy and Gardner were observed at a Detroit hospital in eight years, when a total of 1,777 operations were done. Thus the surgical incidence of carcinoma of the gallbladder was slightly over 1 per cent. In the gastrointestinal tract only the stomach, colon, rectum and esophagus are more often the site of cancer than is the gallbladder. The etiology of carcinoma of the gallbladder is not clear, but the authors feel that the relationship of cholelithiasis to carcinoma deserves special attention. Sixteen of their 19 patients had calculi in the gallbladder. In other reports the incidence of the concurrence of cancer and stones of the gallbladder varies between 36 and 100 per cent. Cholecystitis is invariably present. Eleven of the 19 patients were in the sixth decade of life, when this type of carcinoma is regarded as most frequent. Fourteen of the patients were women, and other literature reports likewise stress the much higher incidence in women than in men. The correct diagnosis was not made preoperatively in any of the 19 cases. Icterus was present in 13 of the 19 cases. Loss of weight is a significant factor. A primary tumor of the head of the pancreas had been suspected in some of the cases; however, in the majority of instances, a diagnosis of chronic cholecystitis and cholelithiasis was given. The authors treated 13 of their 19 patients by cholocystectomy with or without the removal of the adjacent hepatic beds; 5 were treated by cholecystotomy for drainage, and one advanced neoplastic process was treated by a gastroenterostomy. Five of the 16 patients that could be traced were living from eighteen months to seven years after the operation; 1 patient died three years after the operation, and the remaining ones all died within fifteen months. The 5 in whom hepatic metastases were observed at the time of operation all died in less than eight months. In view of the frequent concurrence of cancer with cholelithiasis, the authors regard prophylactic removal of gallbladders harboring stones as imperative.

Yale Journal of Biology and Medicine, New Haven

21:113-180 (Dec.) 1948

Electrophysiologic Methodology for Studies in Neuropharmacology. A. Mauro, A. P. Truant and E. L. McCawley.—p. 113.
Sensitivity of Streptococci to Penicillin G After Exposure to Antibiotic in Vivo. E. Grunberg, C. Unger and D. Eldridge.—p. 121.
*Some Observations on Liver Function Tests. G. Klatskin.—p. 127.
Relationship Between pH Tolerance, Virulence, and Proteolytic Enzymes in Bacteria. I. Bacillus Anthracis. J. M. Leise.—p. 145.
Macrocytic Anemia of Pregnancy: Review of Literature and Report of Case Treated with Folic Acid. S. E. Eisenberg.—p. 161.

Hepatic Function Tests.—Klatskin shows that few of the tests employed actually measure normal physiologic functions of the liver. Thus, while changes in the level of serum albumin and bilirubin or in the excretion of galactose may indicate disturbances in normal functions, the excretion of a foreign dye, such as sulfobromophthalein sodium, cannot be regarded as a measure of any of the normal functions of the liver, even though it may reflect abnormalities in them indirectly. Some of the tests measure changes which, while they may disclose the presence of pathologic processes in the liver, do not necessarily imply any abnormality in its functions. Features of the liver which make it peculiarly difficult to study include the multiplicity of its functions, not all of which are equally or simultaneously affected in disease; its tremendous reserve and regenerative power, which permit extensive damage or removal of tissue before any of its functions are disturbed, and the intimate anatomic relationships of its glandular, excretory and vascular components, which make for complex functional disturbances, even when the initial injury is confined to one component. It is not difficult to understand why early attempts to find a single comprehensive test of hepatic function were bound to fail. The recent trend has been toward the use of a battery of tests. Unfortunately, as the number and sensitivity of the tests increase, they become increasingly difficult to interpret. The author discusses the tests that have been in use at Yale University School of Medicine. He reaches the conclusion that hepatic function tests have their greatest value in the diagnosis of subclinical disease of the liver and in following the course of overt disease of the liver. They are of far less value than are the history, physical examination and other clinical data in the differential diagnosis of outspoken disease and are, at best, confirmatory.

FOREIGN

An asterisk (*) before a title indicates that the article is abstracted. Single case reports and trials of new drugs are usually omitted.

British Medical Journal, London

1:1-42 (Jan. 1) 1949

Clinical and Social Problems of Epilepsy. F. J. Nattrass.—p. 1.
*Antihistamine Drug Treatment of Acute Nephritis. J. Craig, N. S. Clark and J. D. Chalmers.—p. 6.
Cerebral Embolism Following Contusion of Heart. G. Parsons-Smith and D. Williams.—p. 10.
Antihistamine Drugs in Treatment of Nausea and Vomiting Due to Streptomycin. J. R. Bignall and J. Crofton.—p. 13.
Tetany Following Removal of Parathyroid Adenoma with Bone Disease: Finally Alleviated with Calciferol. Nancy S. Conway.—p. 14.
Agglutinin Anti-P in Pregnancy: Report on 2 Cases. I. Dunsford. —p. 15.
Human Louse in Transmission of T. Duttoni in Nature. R. B. Heisch. —p. 17.
Meningococcal Conjunctivitis. J. D. A. Gray and R. A. Lambert.—p. 17.

Antihistamine Drug in Acute Nephritis.—Craig and his co-workers point out that the tendency for acute nephritis to occur at an interval of a week or two after an acute bacterial infection suggests that nephritis may be in the nature of an allergic response to bacterial toxins. The relationship which seems to exist between acute nephritis and some cases of anaphylactoid purpura lends further support to this theory. The authors tested the effect of antihistamine drugs in patients with acute nephritis. They give an account of 8 cases in which they used the antihistamine drug pyranisamine maleate (anthisan,® neoantergan maleate®). They compare the course of these cases with that of 9 consecutive cases of acute nephritis treated in the same hospital during the period immediately preceding the institution of this treatment. The duration of activity of the disease, as assessed by abnormal findings in the urine, is notably shorter in the cases in which treatment is with pyranisamine maleate than in those of the control group. The antihistamine drug was given in doses of 0.1 Gm. three times a day. The authors have formed no definite opinions on optimum dosage or duration of treatment. In some cases the administration of the drug was stopped when all abnormal signs disappeared; in others it was continued for a further week or two. They feel that since acute nephritis is a disease which may run a variable course, no final evaluation of the described treatment is possible on the basis of the small number of cases.

Guy's Hospital Reports, London

97:1-131 (Nos. 1 and 2) 1948. **Partial Index**

*Blalock-Taussig Operation for Morbus Caeruleus. M. Campbell.—p. 1.
Anesthesia for Operations for Relief of Congenital Pulmonary Stenosis. E. H. Rink, P. J. Helliwell and A. M. Hutton.—p. 48.
Four Cases of Polypoid Tumor ("Myxoma") Within Left Auricle of Heart. T. B. Brewin.—p. 64.
Studies in Lung Abscess. R. C. Brock.—p. 75.

Blalock-Taussig Operation for Morbus Caeruleus.—Campbell describes the steps that led to the development of the Blalock-Taussig operation for cyanotic congenital heart disease and says that the fundamental requisite for success is that the cyanosis and disability should be mainly due to an inadequate blood flow to the lungs. The first 18 patients chosen at Guy's Hospital and operated on by Blalock or by Brock are described. The main features on which these patients were selected were persistent cyanosis from infancy with polycythemia and clubbing of the fingers and severe disability on walking. On radioscopy the heart showed little or no general enlargement, though most patients had some enlargement of the right ventricle. Most of them had a systolic murmur in the pulmonary area, often with a slight thrill. All were of normal mental development, but most were under weight. Squatting was noted in four fifths and panting after exertion was nearly as characteristic. The operation was usually an end to side subclavian-pulmonary anastomosis on the side opposite to the aortic arch: this was right-sided in one quarter. The immediate upset caused by the operation is less than might be expected. Three of the 18 died; 1 could not have an anastomosis done, and 1 did not benefit much. The remaining 13 were enormously improved almost at once, and the improvement has been maintained or increased for the three to six months that have elapsed since the operation. The polycythemia disappeared quickly and the clubbing of the fingers more slowly. Fallot's tetralogy seems the probable diagnosis in about three quarters of the cases of congenital heart disease in which cyanosis dates from birth or early in life. The high mortality without operation justifies the risk involved in the Blalock-Taussig operation. Auricular septal defect (combined with some other defect causing cyanosis from birth or soon after) seems to be the commonest abnormality contraindicating operation. The condition of the pulmonary arterial branches in radioscopy is the most essential part of the examination. In a doubtful case cardiac catheterization and angiocardiography should be decisive.

Journal of Tropical Medicine and Hygiene, London

51:243-262 (Dec.) 1948

Remarks on Common Ulcers of Leg in Tropics and Subtropics with Description of Tropicaloid Ulcer (Mycetoid Desert Sore). A. Castellani.—p. 245.
Normal Hematological Standards for Nairobi, Kenya. J. I. Roberts. —p. 254.
*Experiments on Standardization and Keeping Properties of Tetanus Antitoxin in the Tropics. R. K. Goyal.—p. 259.

Standardization and Keeping Properties of Tetanus Antitoxin.—Goyal presents studies which indicate that it is not possible for a drug control laboratory to determine the exact unitage of any sample of tetanus antitoxin, unless a standard toxin or a standard strain of the Clostridium tetani is used. It might not be convenient to compel all laboratories and manufacturing concerns throughout the world to use a particular toxigenic strain of Cl. tetani for production of toxin; it should, however, be possible to lay down the use of a selected strain by all the manufacturers in India to enable the standardization laboratories to arrive at a reliable and satisfactory figure with regard to the unitage of tetanus antitoxins. The possibility of variation due to the use of a heterologous test toxin for titrating imported tetanus antitoxin cannot be ruled out in the absence of a concerted international agreement about the universal employment of a standard strain for toxin manufacture. Discussing the keeping properties of tetanus antitoxin serums, the author says that manufacturers add an extra unitage at the time of issue of antitoxins to allow for deterioration during storage. It appears that the extra unitage allowed for is not calculated on any scientific basis. The author titrated a number of samples of tetanus antitoxic serums with the same toxin at various intervals. He found that the rate of deterioration is apparently affected by the physical properties of the serum, which are dependent to some extent on the method of concentration. The rate of deterioration of the serum in the case of the enzyme-disaggregated product (RD-244-D) was much less than in serums concentrated by ammonium sulfate. In temperate countries, extra unitage is allowed on the basis of 10 per cent per year deterioration of the serum. On titration of eight samples of antitoxic serums obtained from England and Australia, an extra unitage of 25 per cent to 80 per cent was found. Since in India antitoxin has been noted to deteriorate at the rate of 24 per cent per year, the author believes that Indian manufacturers should add at least 30 per cent extra unitage for each year of storage.

Lancet, London

1:1-46 (Jan. 1) 1949

Consciousness and Its Disturbances Considered from Neurologic Aspect. J. P. Martin.—p. 1.
Hirschsprung's Disease and Idiopathic Megacolon. M. Bodian, F. D. Stephens and B. C. H. Ward.—p. 6.
*Intravenous Treatment of Anemia with Iron-Sucrose Preparation. H. G. B. Slack and J. G. Wilkinson.—p. 11.
Intravenous Iron in Treatment of Anemia of Pregnancy. A. D. T. Govan and Jean M. Scott.—p. 14.
Response of Infants to Diphtheria Immunization. B. Vahlquist.—p. 16.
Gastric Biopsy: Report on 55 Biopsies Using New Flexible Gastric Biopsy Tube. I. J. Wood, R. K. Doig, R. Motteram and A. Hughes. —p. 18.
Preliminary Trials of Bistrimethylammonium Decane and Pentane Diiodide (C10 and C5) in Man. G. Organ, W. D. M. Paton and E. J. Zaimis.—p. 21.

Iron-Sucrose Preparation for Intravenous Use.—Slack and Wilkinson describe a method of preparing an iron-sucrose preparation which contains 2 per cent of elemental iron and which they have given intravenously in repeated doses to over

120 persons. They report on the hematologic responses of the first 60 patients with iron deficiency anemia. About a third of these have been treated with the aforementioned preparation, and the remainder have had another form of iron-sucrose preparation. There has been no detectable difference in tolerance or response in many batches of either of these two preparations. The authors gained the impression that these iron-sucrose preparations are relatively safe and effective vehicles for giving iron parenterally. Reactions, if any, were mild, and only four small local venous thromboses have occurred in over eight hundred injections. The authors conclude that these two preparations will be valuable in the treatment of iron deficiency anemia that has proved refractory to iron given by mouth, or of patients who do not tolerate iron by mouth in adequate doses.

Medical Journal of Australia, Sydney

2:733-760 (Dec. 25) 1948. **Partial Index**

Transuterine Injection of Lipiodol in Treatment of Sterility. R. F. Matters.—p. 740.
Addison's Disease: Report of a Case with Unusual Features and Review of Thirty Cases. A. J. Barnett.—p. 742.
Values for Mineral Content of Serum of Australian Adults. Beryl Splatt.—p. 744.
Hemophilus Influenzae Meningitis in 40 Infants Treated with Sulfonamides, Type-Specific Antiserum and Penicillin at Children's Hospital, Melbourne. Elizabeth K. Turner.—p. 745.

Paris Médical

2:529-540 (Dec. 18) 1948

Gynecology in 1948; Annual Review. R. Palmer.—p. 529.
Clinical Diagnosis of Hormonal Condition of Ovaries. P. Mocquot.—p. 532.
*Metastasis of Cancer of Breast to Ovary. A. Ameline and Y. Chatain.—p. 536.

Ovarian Metastasis.—Ameline and Chatain report 1 case of bilateral ovarian metastasis of cancer of the breast in a woman aged 58. Radical amputation of the breast including dissection of the axilla was performed in March 1945. The patient was followed up to May 1948, when she complained of hypogastric heaviness. In the pelvis two hard, mobile masses were observed on palpation. Laparotomy revealed two enormous ovarian tumors and infiltration of the utero-ovarian pedicles. Low subtotal hysterectomy was performed. Microscopic examination of the specimen revealed ovarian tumors of polymorphous, extremely atypical malignant type with spread of the neoplasm to the uterus associated with uterine endometriosis. In August 1948 the patient's condition was still satisfactory but prognosis highly unfavorable. Total hysterectomy with removal of the adnexa rather than subtotal hysterectomy is the treatment of choice for ovarian metastasis spreading to the uterus. Castration should be performed in all cases of inoperable cancer of the breast, and surgical intervention is to be preferred to radiotherapy. In young women with regular menstruation and operable neoplasm of the breast, oophorectomy should be performed provided that the clinical aspect is suggestive of considerable malignancy. Supportive "hormone" treatment is to be considered as still in the experimental stage.

Prensa Médica Argentina, Buenos Aires

35:2313-2340 (Dec. 3) 1948. **Partial Index**

*Juxtacardial Ulcer and Ulcer of Upper Third of Stomach: Surgical Treatment by Kelling-Madlener's Operation. A. Reccius.—p. 2313.
*Clinical Aspects of Cardiovascular Brucellosis. I. Maldonado-Allende.—p. 2323.

Juxtacardiac Ulcer.—Reccius shares Kelling's opinion that a successful surgical treatment of juxtacardiac ulcer, after failure of medical treatment, does not necessarily consist of the removal of the ulcer but of creating favorable local conditions for the healing of the ulcer. The operation which possesses the necessary requirements is the so-called palliative resection of the antropyloric region of the stomach. The author resorted to antropylorectomy by Kelling-Madlener's technic in 24 patients. The operation was performed without touching or cauterizing the ulcer. There were neither postoperative complications nor death. The gastric disorders disappeared rapidly and permanently. Fourteen of the patients were followed up for three to fourteen years. Ten had had the operation in the last two years. The clinical symptoms disappeared in all patients. Repeated roentgen examinations showed disappearance of the niche. The author concludes that palliative resection by Kelling-Madlener's technic is indicated in juxtacardiac ulcer, in ulcer of the upper third of the lesser curvature and in ulcer of the cardiac portion of the stomach. The results of the operation, both immediate and permanent, in all the patients observed by the author were excellent. This operation is to be preferred to a gastroenterostomy.

Clinical Aspects of Cardiovascular Brucellosis.—Maldonado-Allende observed 428 cases of brucellosis in the course of the last five years in patients cared for at the Hospital Argentino de Clínicas and in the Centro Cardiológico Nacional. Brucella lesions of the cardiovascular system were encountered in 55 cases in the group. The cardiovascular disorders were predominantly brucellar in 47 cases. There was chronic brucellosis in 36 cases, acute brucellosis in 6 cases and subacute brucellosis in 6 cases. The following cardiovascular disorders were encountered: branch block in 6 cases, arborization block in 1, auriculoventricular block in 1, subacute coronary insufficiency in 3 and myocardial infarction in 2. Extrasystolic arrhythmia was frequent, being the predominant complaint of 4 patients. There was fibrillation in 2 cases. Aortitis was present in 2. Among the group of patients under 40 years of age arterial hypotension was encountered in 12 and hypertension in 22. Tachycardia was present in all cases of brucellosis, acute or subacute. In chronic forms of the disease with cardiovascular complication tachycardia was so constantly encountered as to be considered of diagnostic value. Auricular paroxysmal tachycardia was present in 1 case. There was constant and pronounced neurocirculatory asthenia in 4 cases. Endocarditis was not present in any case. The author emphasizes the need of directing attention to the brucellar causation of pericarditis in cases of the disease of obscure origin. The pericardium may be involved in a similar manner as the pleural serosa. The involvement of the myocardium, rather than of the endocardium, is the most frequent cardiovascular complication of chronic and acute brucellosis. Reversibility of the cardiovascular symptoms was rare and only temporary. Cardiovascular complications of brucellosis constitute a clinical cardiac form of brucellosis, which calls for diagnosis in cases of cardiovascular disease of unknown etiology.

Presse Médicale, Paris

56:897-908 (Dec. 25) 1948. **Partial Index**

Value of Respiratory Type as a Secondary Sexual Character in Adults. E. May.—p. 897.
*Place to be Given to Adrenalectomy in Treatment of Arteritis. L. Leger, A. Mathivat and S. Tchékoff.—p. 898.
Volatile Antibiotics; Beta-Antibiotics. W. N. Markoff.—p. 901.

Adrenalectomy for Arteritis.—Leger and his co-workers performed adrenalectomy on 25 patients between the ages of 31 and 64 with arteritis. There was no operative death. No signs of cortical insufficiency were observed in the patients operated on. On the contrary, functional improvement was superior to that obtained by drugs or other surgical interventions. Thirteen of the 25 patients were followed up for two years. Good results were obtained in 8 patients, medium results in 2 and 3 were failures. Not one of the 13 patients had to undergo postoperative amputation, and even in those with medium results and in the failures there was no progression of the pathologic process and the lesions were stabilized. Although adrenalectomy may not be the method of choice in all cases of arteritis, the results obtained with this method in young and middle-aged patients warrant its employment, particularly in those in whom the gangrenous lesions are little advanced and the arterial involvement still shows a tendency to spasms. Adrenalectomy should not be practiced in cases in which the spasmodic element has given place to organized thrombosis. In patients of advanced aged intervention on the sympathetic nerve should be done first, but in case of failure adrenalectomy may be justified, as in 2 of the author's patients aged 60 and 64 respectively.

Book Notices

A Course in Practical Therapeutics. By Martin Emil Rehfuss, M.D., F.A.C.P., Professor of Clinical Medicine and Sutherland M. Prevost Lecturer in Therapeutics, The Jefferson Medical College of Philadelphia; F. Kenneth Albrecht, M.D., and Alison Howe Price, A.B., M.D., Asst. Professor of Medicine, The Jefferson Medical College of Philadelphia. Cloth. Price, $15. Pp. 824, with 70 plates. Williams & Wilkins Co., Mount Royal and Guilford Aves., Baltimore 2, 1948.

This book is an attempt to collate the essential information that has been gathered over a considerable period in teaching departments at the Jefferson Medical College of Philadelphia. It is intended, as the title suggests, to offer discussions on "the entire field of therapeutics in one volume." The contents include chapters on general therapeutic principles, symptomatic therapy, treatment of specific disorders and special treatment. The editors frankly admit "there is undoubtedly much to criticize," but probably the average person who turns to this book will overlook some of the causes for criticism because of some excellent features, such as the inclusion of plates that permit visual understanding of a variety of perplexing problems, such as headache, chronic nephritis, contact dermatitis, acute pancreatitis and brucellosis. The book could be criticized on the grounds that it is not sufficiently critical of some of the measures that are used—for example, vitamin E—but, on the other hand, it does provide details of technics, such as the administration of heparin, which offer useful information often unobtainable in reference books. If this book goes into a second edition it is likely that some of the causes for criticism will be removed, but even in its present form it undoubtedly will be well received by many who like their information presented in succinct and orderly fashion.

A Textbook of Histology. By Alexander A. Maximow and William Bloom, Professor of Anatomy, University of Chicago. Fifth edition. Cloth. Price, $8.50. Pp. 700, with 562 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London W.C. 2, 1948.

Previous editions of this textbook of histology have been reviewed in THE JOURNAL, and all reviews have been commendatory. The present edition is likewise excellent. The author seems to differ from some other investigators in certain interpretations of histologic and pathologic observations; however, he gives also the point of view of those with whom he may differ. For example, he believes that "the macrophage system" is a more appropriate term than the "reticuloendothelial system," apparently because Metchnikoff was the first to recognize this system of cells, which he called macrophages, as belonging to a single physiologic system and to see clearly the function of these cells in inflammation and immunity. Generally, however, the term reticuloendothelial system as defined by Aschoff has come into more widespread use. The numerous illustrations in this book are outstandingly clear, well selected and informative.

One of the most notable changes in this edition is in the makeup of the book whereby the width of the line of type is only half the width of the lines in the previous edition; that is, each page has two columns instead of being solid as before, and this adds to the ease and speed of reading. A minor oversight in the makeup is the beginning of a paragraph in the last line on the page, which is done in numerous places; for example, pages 87, 111 and 627. This minor point, it seems, could have been readily corrected by a little more supervision of the printers. Another minor oversight appears on page 47, where it is stated that a certain discussion will be found on "page 000." There is no such page in the book.

Study on Vitamin 'P.' Part I: Capillary Permeability and Fragility. By Boris Th. Sokoloff, M.D., Ph.D., Associate Director of Research, and James B. Redd, Ph.D., Director, Citrus School, Florida Southern College, Lakeland, Florida. Florida Southern College, Monograph 1. Paper. Pp. 39, with 3 illustrations. Florida Southern College, Lakeland, Florida, 1949.

This pamphlet presents a discussion of capillary permeability and fragility, and presumably is intended to advance arguments concerning the relation of the so-called vitamin "P" to permeability and fragility of the capillaries.

Education Through Physical Activities: Physical Education and Recreation for Elementary Grades. By Patricia Ruth O'Keefe, Ph.D., Director of Health and Physical Education, and Helen Fahey, A.M., Supervisor of Health and Physical Education, Kansas City, Missouri, Public Schools. Cloth. Price, $4. Pp. 309, with illustrations. C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, 1949.

This book presents a program of physical recreation activities which can be included in elementary school physical education. Purposes of a good program, it is pointed out, must extend beyond exercise to include opportunities for social and recreational learnings as well as for improved mental and emotional health. The authors have attempted to show how the program can be developed on a worth while basis in the many varying situations found in American elementary schools. Attention has been given to the fact that available facilities and space will make a difference in the kind of program that can be conducted.

The material is divided into four sections. The first section is devoted to principles of child growth and development as they apply to physical education and the factors involved in selection of activities and program planning and evaluation. The second part details suggested activities for the outdoor program, including methods of organizing and planning informal play periods and classwork in physical education. Section three is devoted to indoor activities, with emphasis on adapting materials of instruction to the existing situation. Suggestions are outlined for using the classrooms, halls and other available spaces for physical education as a temporary expedient when no gymnasium is available. Both indoor and outdoor activities are grouped in two categories on a grade level basis; namely, those for primary children in grades 1, 2 and 3 and those for intermediate children in grades 4, 5 and 6.

It is hoped that the publication of another guide of this kind will be a stimulus to the development of more effective physical education at the elementary school level. Despite the recognition of both the medical and educational professions that the elementary schools offer the most fertile field for developmental activities, the best programs and best prepared teachers are generally found in the secondary schools.

The book is noteworthy in that an effort has been made to present the materials in a way that will be intelligible to the classroom teacher and lay leader of youth groups, as well as the professionally trained physical educator. While the volume will prove of greatest value as a textbook in teacher education and a guide for teachers and school administrators in service, it will also be of interest to school medical advisers and physicians serving on boards of education or on school health committees.

An Introduction to Dermatology. Formerly by Norman Walker, Kt., M.D., LL.D., and G. H. Percival, M.D., Ph.D., F.R.C.P.E. Eleventh edition by G. H. Percival, Grant Professor of Dermatology, the University of Edinburgh, Edinburgh. Cloth. Price, $9. Pp. 349, with 233 illustrations. Williams & Wilkins Co., Mount Royal and Guilford Aves., Baltimore 2, 1947.

This book offers much more than one could expect from the title. Only the author's clear and concise style has made possible the inclusion of such voluminous material, rarely found in books of this size. The anatomic, biologic, embryologic, physiologic, allergic, bacteriologic, pathologic and endocrinologic basis of the various cutaneous manifestations are dextrously woven into a harmonious clinical pattern easy to comprehend. The common dermatoses are fully described; the rarer ones less completely. The illustrations, many of which are colored, are excellent. The book contains a wealth of practical information as to diagnosis and therapy, seldom encountered in one large dermatologic book. The external treatment of cutaneous disorders is thoroughly discussed and illustrated. Emphasis is also placed on the internal treatment of various dermatoses. Especially stimulating and elucidative is the author's classification and delineation of the complex disease eczema, according to the nature of the precipitating factors, into six types, and the subdivision again of one of the groups, infective eczema, into four main types. The book was written primarily for students and beginners in dermatology. General practitioners will find it a most welcome addition to their libraries.

Queries and Minor Notes

THE ANSWERS HERE PUBLISHED HAVE BEEN PREPARED BY COMPETENT AUTHORITIES. THEY DO NOT, HOWEVER, REPRESENT THE OPINIONS OF ANY OFFICIAL BODIES UNLESS SPECIFICALLY STATED IN THE REPLY. ANONYMOUS COMMUNICATIONS AND QUERIES ON POSTAL CARDS WILL NOT BE NOTICED. EVERY LETTER MUST CONTAIN THE WRITER'S NAME AND ADDRESS, BUT THESE WILL BE OMITTED ON REQUEST.

DAMAGE TO FETUS BY VIRUS INFECTION OF MOTHER

To the Editor:—A healthy young woman, in her third month of a pregnancy, gives a history of having suffered an attack of varicella in the first month of pregnancy. 1. What is the possibility of damage to the fetus by this virus infection? 2. Should termination of pregnancy be considered? 3. Has work been done on the relation between maternal virus infections during pregnancy and congenital defects of the newborn, comparable to the studies which have been performed in rubella? M.D., Puerto Rico.

ANSWER.—A fetus may be damaged by varicella but this is much less likely than is the case with rubella. J. J. Prendergast (*Arch. Ophth.* **35**:39-41 [Jan.] 1946) cited a case of microphthalmus in a fetus following chickenpox in early pregnancy. C. Wesselhoeft (*New England J. Med.* **236**:978-988, 1947) expressed the belief that other diseases than rubella, such as measles, mumps, chickenpox, herpes zoster and influenza, may cause defects similar to rubella in the fetus although less often. 2. In view of the infrequency of fetal anomalies in cases of varicella, an abortion should not be performed. 3. The number of cases of fetal abnormalities associated with varicella is small and no special study has been made. An interesting editorial appears in THE JOURNAL (**138**:653-654 [Oct. 30] 1948) on "Congenital Defects" in which the subject of fetal monstrosities due to the passage of viruses through the placental barrier is discussed.

CARPOPEDAL SPASM

To the Editor:—Recently I was called in to see a 63 year old white Italian man with known hypertension of years' duration. He had suffered some sort of attack while at work associated with fainting which had been diagnosed as a "stroke." When I saw him four hours after this episode he was semicomatose, exhibited Cheyne-Stokes respiration and had a bounding, regular pulse associated with a blood pressure of 230 systolic and 130 diastolic. He also exhibited convulsions, during the cyanotic, apneic phase of his respiratory distress, starting as a lateral deviation of his eyes to the right, deviation of the head to the right, carpopedal spasm on the right and then on the left followed by generalized clonic convulsions. The episode lasted approximately three minutes, ceased, and his color returned to normal. The cycle was repeated numerous times until he died four hours later. It is my impression that thier patient suffered a massive intracranial hemorrhage. I can find reference to everything in this picture except the carpopedal spasm in standard neurologic texts. What other mechanism can be postulated to explain them? How comon are they in adults? Do they occur in any other conditions except tetany?
M.D., Pennsylvania.

ANSWER.—Carpopedal spasm is not a common occurrence in generalized clonic convulsions from cerebral hemorrhage. The most likely explanation is that this man was over-ventilating and had a prolonged overventilation at the peak of Cheyne-Stokes respiration. By this overventilation he produced temporary alkalosis in his blood with the appearance of temporary tetany. During apnea he recovered sufficiently from this alkalosis to stop having tetany. This seems like a possible explanation of this unusual manifestation.

The other possibility is that this was simply extensor rigidity at the beginning of the convulsion, and this would not be so unusual.

TREATMENT OF PIGMENTED MOLE

To the Editor:—Please outline the management of a pigmented mole in a 1 year old child. This mole or nevus is located in the back of the neck and is 1.5 cm. by 1.25 cm. It is colored black and has a small central area which is much darker than the periphery. The central area is the size of a small pea. None of it is elevated or hairy. Is solid carbon dioxide contraindicated? Might such treatment produce malignant reaction? Is excision feasible? Might surgical removal cause a malignant reaction subsequently?
Herbert Kornblitt, M.D., Belmont, Mass.

ANSWER.—The general opinion of dermatologists and oncologists is that black moles should be removed, particularly if they are growing, changing color, if they become inflamed or, as in this case, if they are located on an area that is likely to be irritated repeatedly. There is reason to believe that it is best to remove such moles before the onset of puberty, although the evidence for this view is not conclusive. Surgical excision is preferred rather than removal by solid carbon dioxide. Authorities do not believe that surgical removal will cause the development of cancer later.

SALIVATION IN PARKINSONISM

To the Editor:—I am suffering with postencephalitic parkinsonism and am plagued with excess salivation and inability to swallow. The saliva pours out of my mouth as if from a faucet, making it impossible for me to keep up a conversation. These symptoms exaggerate my tremor. Please suggest treatment.
M.D., Florida.

ANSWER.—The excessive salivation, which is typical of the postencephalitic form of parkinsonism, is usually readily controlled with one of the belladonna-like drugs which are commonly used in the treatment of this disorder. Atropine is often used for this purpose. The dosage has to be adjusted for each case and should be less than that which will produce the toxic or undesirable effects typical of this drug. Many have found vinobel® particularly efficacious in the treatment of this form of parkinsonism. This is an extract of belladonna in tablet form. Small doses, such as 0.4 mg. once a day, should be used at first and then gradually increased until the maximum desirable relief is obtained. It is the usual practice to increase the dose until mild toxic symptoms are produced and then to reduce the dose slightly. Some patients are able to tolerate as much as 0.8 mg. three or four times a day. With the improvement in salivation and in the control of muscular functions which this drug should produce, it is likely that the patient will also have considerable improvement in his ability to swallow.

FISSURED FINGERTIPS

To the Editor:—A female patient, aged 46, suffers mildly from menopausal symptoms. Her chief complaint is development of fissures over the terminal phalanges during the winter months. Some transverse splitting of the nails also occurs. Neurologic or circulatory disturbances are absent, and results of a complete physical examination and laboratory study are within normal limits. Is this condition considered an entity? What treatment has been found effective? John J. Clancy, M.D., Hartford, Conn.

ANSWER.—The condition of cracked fingertips per se does not constitute a dermatologic entity. Fissures on the fingertips occur not infrequently in association with inflammatory diseases, such as psoriasis, eczema-dermatitis or hyperkeratotic tinea; in association with dry skin due sometimes to hypothyroidism, and, more often, as a result of a combination of factors consisting of trauma, strong soaps and washing powders, particularly in cold weather. Hyperkeratotic plaques, which may become fissured, are occasionally observed on the palms or finger tips of women with keratoderma climactericum, the nosologic position of which has not yet been determined. Some dermatologists consider it a variation of psoriasis or neurodermatitis. Relief usually can be obtained by frequent application of a lubricant containing 5 per cent compound Benzoin tincture in cold cream, an oily base or a water-soluble base. In addition, the woman should use only soft water, a soap substitute and protective gloves in her work.

NUCLEUS PULPOSUS

To the Editor:—1. What are the most common causes of ruptured nucleus pulposus? 2. Has bowling ever been known to be the cause of a ruptured disk?
Moody Walker, M.D., Huntsville, Ala.

ANSWER.—The most common cause of ruptured nucleus pulposus is trauma, particularly that which accompanies flexion or torsion of the trunk while lifting heavy weights or pulling against unyielding objects. The onset has often been associated with a patient's falling backward, swinging at an object in an athletic event or stooping to pick an object from the floor. Poor posture and weak paravertebral musculature are believed to be inciting causes.

While specific instances do not come to mind, bowling could cause a herniated nucleus pulposus because of the flexion and torsion of the trunk that it requires. It should not, however, be condemned as an exercise, because it also aids in strengthening the muscles of the back.

PAPILLOMA OF VOCAL CORDS

To the Editor:—A patient (35 years old) has papilloma of the vocal cords. He has been operated on several times without complete success. Is the hormonal treatment of value in males?
M.D., Baltimore.

ANSWER.—Hormonal treatment for papilloma of the vocal cords is of dubious value. As employed by Broyles (*South. M. J.* **34**:239, 1941) in the treatment of laryngeal papilloma in children, therapy consists in the local application of estrogens (1,000 international units) 0.1 cc. to the laryngeal mucosa once each week for approximately six months.